PREMATURE INFANTS

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a manual for physicians

FEDERAL SECURITY AGENCY Social Security Administration CHILDREN'S BUREAU

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by ETHEL C. DUNHAM, M. D.

"In writing the book I have honestly tried to avoid the four grounds of human ignorance set forth so long ago by Roger Bacon: trust in inadequate authority, the force of custom, the opinion of the inexperienced crowd, and the hiding of one's own ignorance with the parading of a superficial wisdom."—J. W. Ballantyne.

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Joreword

Of the 3,000,000 births that occurred in the United States in 1944 approximately 150,000 (5 percent) may be conservatively estimated to have been premature. The death rate among premature infants is high and the cause of death is often obscure. It is known that the less the infant weighs at birth the less is the chance of survival. Prolongation of pregnancy to as near term as possible by all means consistent with the welfare of the mother as well as the infant is the best method of reducing mortality from premature birth. After birth the premature infant requires special care by physicians and nurses with knowledge of the best methods of care and skill in applying them. Studies have shown that the physical and mental development of these infants, provided they have not received a cerebral injury during birth, compares favorably with the development of full-term infants.

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—definition of and criteria for prematurity; incidence, causes, and prevention of premature birth: death rates and causes of death; 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.

My indebtedness to the countless authors and publishers referred to throughout the text, who have kindly allowed me to use their publications in this way, and to the many specialists who have reviewed parts of the manuscript and assisted me with their advice, is obvious. I am particularly indebted to Edward Davens, Louis K. Diamond, Harry H. Gordon, Harriet G. Guild, Everett Kinsey, Howard V. Meredith, Edwards A. Park, John L. Parks, Edith L. Potter, Grover F. Powers, Lewis K. Sweet, Josef Warkany, and the members of the Children's Bureau Pediatric Advisory Committee: Howard Childs

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Foreword

Carpenter, Julius H. Hess, J. H. Mason Knox, and Alfred H. Washburn.

I want especially to thank Isabelle Mott Hopkins, formerly director of the editorial division of the Children's Bureau, who has helped me in every phase of the preparation of this manuscript. Without her tireless and painstaking work my preliminary drafts might never have developed into a manuscript for publication. Acknowledgment is also made to the professional staff of the Children's Bureau, especially the members of the division of reports whose editorial contributions completed the long and complicated process by which such material as mine finally gets into print.

Ethel C. Dunham, M. D.

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PART I

General Considerations

DEFINITION OF PREMATURITY

Prematurity needs to be defined as accurately as possible (1) for correct certification of live births as premature or otherwise; (2) for accurate classification of the causes of morbidity and mortality in the neonatal period; and (3) for legal purposes. Precise definition, however, is impossible because in most cases the exact date when the pregnancy began is not known and because the duration of human gestation has been shown to vary considerably.

The definition of prematurity officially recommended by the U. S. Bureau of the Census as agreed upon by that Bureau, the Children's Bureau, and the American Public Health Association (20, p. 4) is— "the termination of pregnancy in the period from the beginning of the 28th to the end of the 37th week of gestation." The lower limit of 28 weeks is set because it is the consensus that a fetus of less than 28 weeks' gestation has not developed sufficiently for extrauterine survival. The upper limit, the end of the 37th week, is set because the date of beginning of pregnancy cannot be estimated more accurately than within a 2- to 3-week period, and therefore an infant must be born more than 2 weeks before term (defined as 40 weeks) to be considered premature.

The following definition of a live birth has been recommended by the U. S. Bureau of the Census, as agreed upon by that Bureau, the Children's Bureau, and the American Public Health Association (20, p. 4):

"A live-born child is one which shows any evidence of life (breathing, heart beat, or movement of voluntary muscle) after complete birth. Birth is considered complete when the child is altogether (head, trunk,

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and limbs) outside the body of the mother, even if the cord is uncut and the placenta still attached."

Duration of pregnancy is calculated from the date of the onset of the last menstrual period, and the most commonly used estimate is 280 days. Great variation, however, has been found (29, p. 96), even in cases in which the date of "fruitful coition" is known. "Reckoning from this day pregnancy has been found to vary from 220 to 330 days, the average being 270 days." This uncertainty has led to the incorporation in the law of some countries of specified periods within which the legitimacy of a child is recognized, but in the United States "each case is decided on its merits." McCaffrey (58) says, "Fortunate or unfortunate as it may be, there is no definite law laid down in any English-speaking country as to the actual length of the gestation period . . ." After citing cases he comments, "In looking over these cases it is easily seen that judges, juries, and the medical profession vary greatly in their ideas as to the length of the gestation period."

Recognition of prematurity is essential because of the need of the premature infant for special medical and nursing care. Since the definition of prematurity, as usually made, based on calculations of gestation period, is not satisfactory for this purpose, certain objective criteria have been adopted for their clinical value, as indications of the need for this special care. In order to achieve uniformity in the classification of these infants in need of special care, and comparability of statistical data in hospitals and in studies of such infants, the American Academy of Pediatrics (2, p. 117) adopted the following resolution:

"A premature infant is one who weighs 2,500 gm. or less at birth (not at admission) regardless of the period of gestation.

"All live-born premature infants should be included, evidence of life being heart beating or breathing."

OBJECTIVE MEASURES OF PREMATURITY

The diagnosis of prematurity is sometimes based on certain clinical signs which are not objective but reflect the individual physician's training and experience and which may therefore vary rather widely. (See Clinical Appraisal, p. 103.) It is obvious that criteria are needed for the diagnosis of prematurity that are entirely objective.

Among the objective criteria are certain measurements used alone or in combination, such as birth weight, crown-heel length, measurements of the head and thorax, and degree of development of certain centers of ossification. (More detailed discussion of some of these measurements will be found in the section on Physical Growth, p. 53.)

Birth weight

A birth weight of 2,500 gm. (5 lb. 8 oz.) or less, regardless of esti- ν mated period of gestation and other criteria, has been generally recognized (2) as the most practical *clinical* criterion of prematurity—that is, evidence of need for special care—in spite of the fact that some infants of this weight (especially twins) may have reached 10 lunar months of gestational age. There are advantages also in using a single criterion "for statistical purposes and comparison of results of care (2)." Moreover, the weight is easily taken and requires no special skill.

It must be recognized, of course, that infants below a certain gestational age, even if they show signs of life at birth, cannot survive because they are not sufficiently developed. These products of conception are termed abortions. Most States do not require the reporting, as live births or stillbirths, of products of conception of less than 20 to 28 weeks' gestation. Adair (1, pp. 904-905) classifies as previable infants "between 400 and 1,000 gm. in weight, and 28 and 35 cm. in length, or of 22 to 27 weeks' gestation." Since he adds that two of these factors—weight, length, and gestational age—should be utilized in determining viability, an infant weighing less than 1,000 gm. but exceeding 35 cm. in length and 27 weeks in gestational age would be classified as a viable premature infant under his definition.

In view of the records of survival of infants weighing less than $\frac{1,000}{\text{gm}}$ at birth it is obviously impractical to call this weight the lower limit for a viable premature infant. One infant (65) weighing only 14 oz. (397 gm.) on the second day of postnatal life is reported to $\frac{1}{5}$ have survived and to have weighed at 1 year, 13 lb. 12 oz. (6,238 gm.). Certainly it is a misnomer to apply the term "previable" or "nonviable" or "abortion" to this infant and others in the very low weight group, who not uncommonly flout the definitions and grow to maturity. It would be embarrassing for such an adult to find that he had no birth certificate because the attending physician had reported him as an

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"abortion." The beginning of viability therefore cannot be defined within any narrower limits than the range of weights recorded for infants that have proved their viability (ability to live) by surviving.

Though for practical purposes the use of weight alone as a criterion of the type of care needed and as a statistical standard has the acknowledged advantages mentioned, research looking toward more precise definition must take into consideration many other factors, which will be discussed in the following pages.

Crown-heel length

Crown-heel length at birth has been used as a criterion of prematurity, alone or combined with birth weight. The exact length below which an infant is to be considered premature has been stated differently by different observers. A crown-heel length between 35 and 47 cm. is frequently used as a criterion, in connection with one or more other criteria, for a "viable" premature infant. Measurement of crown-heel length requires considerable skill, and wide discrepancies have been found when the measurements made by clinicians were compared with those made by anthropometrists.

Weight and crown-heel length

Crown-heel length and weight combined have been used as a criterion of prematurity. Reiche (78) found that a group of 14 infants weighing 800 to 1,200 gm. measured 32 to 40 cm. and a group of 23 infants weighing 2,000 to 2,500 gm. measured 41.5 to 50.0 cm. According to his observations, a weight of 1,000 gm. corresponded approximately to a length of 34 cm. and to a fetal age of 27 to 28 weeks. Ylppö (107, p. 124) calls attention to the great variation, sometimes amounting to more than 100 percent, in the weights of premature infants of a given length. For his group of 700 premature infants he gives the following figures for the upper and lower weight limits among infants of each length from 32 to 45 cm.

32 33 34 35 36 37 38 39 40 41 42	cm	600- 760- 750-1, 750-1, 900-1, 690-1, 700-1, , 050-1, 980-1, 350-2, 250-2.	870 860 010 200 140 500 670 700 840 170 200	gm. gm. gm. gm. gm. gm. gm. gm. gm. gm.
40 41	cm1	980-1, 350-2	840 170	gm.
42	cm 1,	250-2,	200	gm.
43	cm 1,	440-2,	050	gm.
44	cm1,	270–2,	300	gm.
45	cm 1,	100–2,	350	gm.

"Thus even in fetal life," he says, "we have to deal with infants who may be thin and long or short and broad."

In the system of classification worked out by Potter and Adair (76, p. 31) the maximum length in the range for viable premature infants is 46.9 cm. and the maximum weight is 2,499 gm.; the corresponding minima are 35.0 cm. and 1,000 gm.

Peckham (70) made a statistical analysis of Johns Hopkins Hospital birth records for a 40-year period (1896–1936), classifying the infants as premature, first according to a weight of less than 2,500 gm. but with a length of at least 35 cm. and then according to a length of less than 45 cm. but with a weight of at least 1,500 gm. (Infants weighing less than 1,500 gm. and also measuring less than 35 cm. were excluded as "abortions" in accordance with the definition in use at Johns Hopkins Hospital at that time.)

Of the 39,394 infants in the series, 4,055 (10.3 percent) were classified as premature according to weight and minimum length and only 2,415 (6.1 percent) were so classified according to length and minimum weight. The author states (70, p. 476) that among the single-born infants "a weight incidence comparable to 45 cm. length fell between 2,200 and 2,300 gm." and refers (p. 490) to "the inaccuracy of criteria for prematurity which now link a weight of 2,500 gm. and 45 cm. together." Not only should standards for weight and length be reviewed, he concludes, but consideration should be given to race, age, and parity of mother, multiple births, and sex of infant.

Weight, length, and gestation period

For their classification of all products of conception from abortions to postmature infants Potter and Adair (76, p. 31) give figures for range in length, weight, and gestational age in five groups and assign each infant to the group in which two of these three criteria fall. They classify infants as previable if they are within two of the following ranges: length, 28.0 to 34.9 cm.; weight, 400 to 999 gm.; gestational age, 22 through 28 weeks. Infants are classed as viable prematures if they are within two of the following three ranges: length, 35.0 to 46.9 cm.; weight, 1,000 to 2,499 gm.; gestational age, 29 through 38 weeks.

Cook (27, p. 211) found that in a series of measurements of 77 premature infants "the shortest infant in the series was 31 cm. long at birth and survived." On the other hand, the youngest infant to survive "was born at 6 months according to the history, although the birth weight was 1,740 gm. and length 41 cm."

Meredith (60) has critically reviewed North American studies on growth in length from birth to 2 years. In regard to growth in stature of premature infants he points out first the great variation in criteria for diagnosis of prematurity. He states (p. 70) that "probably the procedure most widely employed is that of regarding all infants weighing less than 2,500 gm. as premature. . . The stature zone considered indicative of prematurity ordinarily is assigned an upper limit between 45.0 cm. and 47.0 cm." "One needs," he continues, "but a limited knowledge of individual differences in stature for age, or weight for stature, in order to appreciate that age, weight, and stature are not strictly interchangeable media." He cites, for example, a series of 10,660 consecutive births analyzed by Swanson and associates (97), of which 752 were classified as premature by one or more of the three criteria weight, crown-heel length, and gestation period. Of these premature infants 30.1 percent were so classified by weight (2,500 gm. or less) but not by age (37 weeks or less); 23.8 percent by stature (47 cm. or less) but not by age; 9.8 percent by weight but not by stature; 12.9 percent by stature and age but not by weight; 6.3 percent by weight but not by stature or age.

Measurements of the head

Among measurements of the head, the occipitofrontal diameter and circumference are those most often used, alone or in combination with some other criterion. They are used to determine the maturity of the newborn infant and the relation of head size to size of pelvic outlet, and to aid in the early diagnosis of hydrocephalus and microcephalus.

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OCCIPITOFRONTAL DIAMETER

Obstetric textbooks set the occipitofrontal diameter at term as 11.75 cm. to 12.2 cm. Figures for the occipitofrontal diameter of the head at different gestation periods, or according to birth weight or length, show considerable variation. This is to be expected because of the effects of molding during birth, edema, and hemorrhage into soft tissues, and because of lack of precise definition of the anatomical points from which measurements are taken.

Scammon and Calkins (86, pp. 96–97) have reported the mean occipitofrontal diameters of the heads of 369 dead fetuses and infants according to body length. The range for a mean length of 47.14 cm., about the length often taken as the upper limit for premature infants, was 9.9 to 12.3 cm. in 24 cases, the mean being 10.92 cm. When allowance was made for birth molding the authors' calculated mean for this length was 11.48 cm. This figure is comparable with the actual measurements made by these authors of 5 living premature and 27 full-term infants with unmolded heads.

The data obtained from both dead and living infants indicate that an occipitofrontal diameter of 11.5 cm. or less suggests prematurity.

CIRCUMFERENCE

The average occipitofrontal circumference (the largest horizontal circumference) of the head of mature newborn infants is usually stated in obstetric textbooks to be 34 to 35 cm. Meredith (61), who reviewed North American studies of head size in the first 2 years of life, appearing from 1850 to 1945, states the composite mean head circumference at birth of the 2,484 white full-term male infants included in these studies as 34.5 cm. and of the 2,483 white female infants, as 33.9 cm. For a mean crown-heel length of 47.14 cm. Scammon and Calkins (86) noted an observed range in head circumference from 28.8 to 36.4 cm. in 24 cases, an observed mean of 32.29 cm., and a mean of 33.12 cm. as calculated to allow for birth molding. The 3 living premature infants with unmolded heads that they measured who were of approximately this length measured 32.6, 32.4, and 32.0 cm. in head Ylppö (108) found that the average circumference circumference. of the head of 100 newborn infants weighing between 3,000 and 3,500 gm. was 33.5 cm. For premature infants (infants weighing 2,500 gm. or less) in four birth-weight groups he found the average head circumference to be between 25.0 cm. in the lowest weight group and 32.3 cm. in the highest. Measurements taken by Reiche (79) for the weight groups 1,500 to 2,000 gm. and 2,000 to 2,500 gm. (the only groups comparable with Ylppö's) closely approximate those of Ylppö.

There appears to be agreement that a head circumference of less than 33 cm. probably indicates prematurity.

Circumference of thorax

Taylor (99) gives the average circumference of the thorax at the nipple line in mature newborn infants as 32.3 cm. for males and 32.1 cm. for females; Ylppö (108) gives 31.0 cm. as the average for full-term infants weighing 3,000 to 3,500 gm. For premature infants the average thorax measurement ranged from 20.8 to 29.5 cm., depending on the degree of prematurity, according to Ylppö (108), and from 22.5 to 28.4 cm., according to Reiche (79).

From the small amount of data available it appears that an infant is probably premature if at birth the thorax at the nipple line measures less than 30 cm., but this measurement alone should not be used as a criterion.

Relation of thorax to head circumference

Disproportion between the circumference of the head and that of the thorax is generally recognized as a sign of prematurity that is more reliable than either measurement alone. Among full-term infants the average thorax circumference was found by Taylor (99), Zeltner (110), and Ylppö (108), respectively, to be 93–94, 94, and 92.5 percent of the average head circumference. Among premature infants the range in different weight groups was from 77.0 to 91.3 percent according to Ylppö, and from 84.0 to 89.8 percent, according to Reiche (79).

Zeltner (110) found that the average difference between the head and thorax circumference was 2.13 cm. in full-term infants and 3.45 to 4.07 cm. in premature infants.

A ratio of thorax to head circumference of less than 93 percent or a difference between head and thorax measurements of more than 3 cm. probably indicates prematurity.

Development of centers of ossification

Roentgenographic demonstration, immediately after birth, of the presence or absence of certain ossification centers might be expected to be useful as an objective method of assessing the degree of prematurity.

Reports of a number of studies of this kind are available, but conclusions as to the time of appearance of any one center and its significance as a sign of prematurity are confusing rather than helpful. In the first place the wide variation in development of the centers in male and female infants and in white and Negro infants pointed out many years ago by Hess and Weinstock (48) has usually not been given consideration; in the second place most studies have been made of full-term infants, and if a center is found present in a full-term infant at birth there is obviously no evidence that it did not appear at a much earlier period.

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With a view to obtaining basic data on the time of appearance of certain centers of ossification in premature and full-term infants. Christie and his coworkers carried out a study of 10 centers of ossification in 1,107 consecutively born premature and full-term infants in the ward service of Johns Hopkins Hospital (A. U. Christie, M. D., unpublished data, U. S. Children's Bureau). The roentgenograms were inade within 72 hours after birth. From the data on the 10 centers 3 were selected (the proximal tibial, the cuboid, and the capitate) because they were the only ones the presence or absence of which appeared to be of clinical significance. The infants studied were divided into two birth-weight groups-those weighing less than 2,000 gm. and those weighing 2,000 to 2,499 gm. (The infant's chances for survival are five to six times greater in the latter group than in the The findings for these 3 centers are shown in table 1, by former.) weight groups and by race and sex.

 TABLE 1
 Number of premature infants with specified centers present, by birth weight and by race and sex (U. S. Children's Bureau)

	Infants w than 2	eighing less ,000 gm.	Infants weighing 2,000– 2,499 gm.		
Ossification center, race, and sex	Total number	Number with center present	Total number	Number with center present	
Proximal tibial					
Males. Females.	11 6	0 0	16 24	3 13	
Males Females	11 14	0 2	26 32	10 13	
Cuboid					
Males Females	11 6	0	16 24	1 9	
Negro: Males. Females.	11 14	03	26 32	6 12	
Capitate					
White: Males. Females.	11 6	0	15 24	0	
Negro: Males Females	11 14	0	26 32	2 4	

It can be seen that the race and sex differences pointed out by Hess and Weinstock were confirmed. Among those weighing less than 2,000 gm. no white infant and no Negro male infant had any one of these three centers present. Among infants weighing 2,000 to 2,499 gm., these centers, except the capitate in white infants, were present in varying proportions in all of the cases. For Negro female infants the presence of the centers for the proximal tibial and the cuboid cannot be considered evidence that they weigh 2,000 gm. or more, for in the group weighing less than 2,000 gm. 2 of 14 Negro female infants showed the proximal tibial center and 3 of 14 Negro female infants showed the center for the cuboid.

In general, the most useful center for distinguishing between the two weight groups (with the exception of the Negro female infants) appears to be that for the proximal tibial epiphysis; that for the capitate is the least useful; that for the cuboid is intermediate. In regard to the value of postnatal roentgenographic demonstration of these centers in determining maturity and in diagnosing endocrine disorders, the wide variation in development, not only between race and sex groups but among individual infants, does not allow any closer approximation to gestational age than does birth weight, alone or combined with crown-heel length.

It is possible, however, that the roentgenographic demonstration of the proximal tibial epiphysis in utero might be used to prognosticate fetal weight. The absence of this center would indicate that the weight was probably less than 2,000 gm. The obstetrician, using his best judgment in regard to the mother's welfare, might then make an effort to prolong pregnancy until the fetus reached a weight more favorable to its survival. Clifford uses the diameter of the fetal head, measured from intrauterine roentgenograms, for this purpose. Ince, however, questions the value of this measurement in estimating the weight and maturity of an individual infant. (See p. 72.) Whether demonstration of the presence or absence of the proximal tibial epiphysis is a more reliable method for determining fetal weight in utero than head diameter remains to be studied.

It should be pointed out that placental blood supply influences the development of the ossification centers. It has been observed that twins who are of the same gestation period but not of the same birth weight show differences in the appearance of the ossification centers, the smaller twin having less advanced osseous development.

It is fortunate that the proximal tibial epiphysis appears to be the center that gives the sharpest differentiation between clinically significant birth weights, because it would probably be more easily identified in roentgenograms of the fetus in utero than either the center for the cuboid or the center for the capitate.

Summary

Because estimation of the duration of pregnancy cannot be exact the physician must usually depend, for his diagnosis of the infant's maturity, on weight and on certain measurements that are more objective criteria than are clinical signs. The criteria that, alone or in combination with one another or with gestational age, have been found to indicate or at least suggest prematurity are:

A birth weight of 2,500 gm. (5 lb. 8 oz.) or less.

A crown-heel length of 47 cm. ($18\frac{1}{2} \text{ in.}$) or less.

An occipitofrontal diameter of the head that is 11.5 cm. $(4\frac{1}{2}$ in.) or less.

A head circumference of less than 33 cm. (13 in.).

A thorax circumference of less than 30 cm. (about $11\frac{3}{4}$ in.).

Disproportion between head and thorax circumference.

The single criterion of prematurity that has been most generally used is a weight of 2,500 gm. (5 lb. 8 oz.) or less. The weight is easily taken and, although not an exact indicator of prematurity, has provided a satisfactory criterion of the need for special care, as well as a uniform basis for statistical analysis. Measurements of crown-heel length tend to be inexact unless made with anthropometric techniques and by skilled individuals. Wide variations have been found in weights of premature infants of a given length.

When weight, length, and gestation period combined are used to determine prematurity the proportion of premature infants so classified differs widely from the proportions found by using any one or two of these criteria. The use of any two of these three criteria in determining prematurity has been advocated.

The circumference of the thorax at the nipple line should not be used alone as a criterion of prematurity, but it is significant in relation to head circumference. An excess of head circumference over thorax circumference of more than 3 cm. or a ratio of thorax to head circumference of less than 93 percent probably indicates prematurity.

Roentgenographic demonstration of development of centers of ossification is of little value in determining degree of prematurity except within wide limits. This is due to sex and race differences in the age of appearance of the centers which usually have not been taken into account in accumulating developmental data.

The center for the proximal tibial epiphysis has been found the most useful center for differentiating premature infants that are approaching maturity from those of lower birth weight. If a roentgenogram of the fetus in utero is taken to determine whether or not this center is present it might provide a basis for predicting whether the infant would weigh more or less than 2,000 gm. That is, the absence of this center would indicate that the weight would probably be less than 2,000 gm.

INCIDENCE OF PREMATURE BIRTH Estimated number

The number of premature births that occur each year in the United States is not known, since the National Office of Vital Statistics does not tabulate the data from item 7—the number of months of pregnancy—on the standard birth certificate. (See appendix 2, facing p. 365.)

It is possible, however, on the basis of findings of special studies, to estimate the number of premature births. For example, in a Children's Bureau study (105) published in 1925, based on nearly 23,000 records of live births in 8 cities, it was found that 5 percent of the births were reported to have occurred after a gestation period of 8 calendar months or less. If 5 percent of the approximately 3,000,000 live births in the United States in 1944 were premature the number of premature infants born in that year was approximately 150,000.

In a more recent report analyzing data taken from birth certificates, 4.4 percent of the live-births to resident mothers (more than 250,000) occurring in a 3-year period (1936-38) in New York State (exclusive of New York City) were stated by the physician to be premature (106, pp. 1012, 1022). A much higher incidence (10.7 percent) may be calculated from the figures given by Eastman (35, p. 350) for total live births and premature live births (infants weighing 1,000 to 2,499 gm.) at Johns Hopkins Hospital during a 20-year period, but about 60 percent of these premature infants were Negroes, among whom the incidence of low birth weight is known to be higher.

The proportion of infants of low birth weight is very much higher among plural-born than among single-born infants; but since the number of plural births, according to the National Office of Vital Statistics, constitutes only 2 percent of the total number of births, it is not necessary for practical purposes to consider data in regard to plural births separately from those in regard to single births.

In considering the incidence of premature birth it is important to note that among infants weighing less than 2,500 gm. the proportion of those in the lower birth-weight groups is much smaller than of those in the higher birth-weight groups. This is shown both in the 1939 series for the whole of New York City studied by Duffield and associates (32) and in figures for 1945 for hospital births in New York City (personal communication from Leona Baumgartner, M. D., City of New York, Department of Health, April 15, 1946). (See table 2.)

Age and parity of mother

That the mother's age and the order of birth influence prematurity was pointed out by Woodbury (105), who found in an analysis based on nearly 23,000 records of infants born in 8 cities that a markedly

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• Weight group	New York	City, 1939	Hospital births, New York City, 1945		
8	Number	Percent	Number	Percent	
Total	7, 291	100.00	10, 244	100.00	
Less than 1,000 gm 1,000-1,499 gm 1,500-1,999 gm 2,000-2,499 gm	370 582 1, 326 5, 013	5.07 7.98 18.19 68.76	457 700 1, 824 7, 263	4. 46 6. 83 17. 81 70. 90	

TABLE 2Number and percentage of premature infants, by birth-weight groups;
New York City, 1939 (Duffield and associates), and hospitals in New
York City, 1945 (Department of Health)

larger proportion of premature births was found among births to the younger than among those to the older mothers (8.6 percent among mothers under 20, decreasing to 4.1 percent for mothers 35 to 39, and then increasing to 4.8 percent for mothers 40 and over). A larger proportion of first births than of births of any later order were premature. In their study of 2,373 single live-born infants, of whom 206 weighed less than 2,500 gm. (5 lb. 8 oz.), Anderson and assocates (5) also found the highest percentage of premature infants among mothers 15 to 19 years old and among primiparae.

Effect of race or economic status.

A Children's Bureau study (33) reported in 1939 showed that in a series of approximately 3,000 live births the percentage of infants of low birth weight (less than 2,500 gm., or 5 lb. 8 oz.) varied with race and sex (6 percent among white male and white female infants; 8 percent among Negro male infants and 14 percent among Negro female infants). These findings were confirmed in the study (32) of more than 100,000 births that occurred in New York City during 1939. Of 99,700 infants weighed at birth, 7.3 percent weighed less than 2,500 gm. The proportion weighing less than this amount varied widely in the race and sex groups studied, as well as in relation to whether the births were single or plural, as is shown in table 3.

	Live births			
Plurality of birth, sex, and race		Birth weight less than 2,500 gm.		
		Number	Percent	
Total with weight stated	99, 700	7, 291	7.3	
Single-born infants: White males. White females. Colored males. Plural-born infants:	46, 574 43, 757 3, 719 3, 683	2, 504 2, 876 320 475	5. 4 6. 6 8. 6 12. 9	
White males. White females. Colored males. Colored females.	885 933 90 59	457 572 56 31	51.6 61.3 62.2 5 2.5	

 TABLE 3
 Incidence of underweight among single-born and plural-born infants, by sex and race; New York City, 1939 (Duffield and associates)

The difference in the proportions of white and Negro infants weighing less than 2,500 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, Brown, and Lyon (6), however, suggest 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 (18) these authors presented data that they consider justification for lowering from 2,500 to 2,350 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 well mothers and for those who had some complications of pregnancy. (See table 4.) This study was based on 1,259 live-born premature infants (580 white and 679 Negro infants weighing less than 2,500 gm.) in a series of 13,526 consecutive single births.

TABLE 4 Incidence of premature births to white and Negro women according to
type of maternal history and specific criteria of prematurity (Brown,
Lyon, and Anderson)

	Live-born premature infants						
	White Birth weight less than 2,500 gm.		Negro				
Mothers			Birth weight less than 2,500 gm.		Birth weight less than 2,350 gm.		
	Number	Percent	Number	Percent	Number	Percent	
Total	580	8	679	12	459	8	
Normal maternal history Maternal history with illness or abnormal- ity	201 379	5 12	244 435	9 14	145 314	5 10	

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 the white mothers, as well as of the Negro mothers, were employed, the Negro mothers may have worked longer hours and for a longer period, 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. The physician will have to decide in treating each case whether or not a Negro infant at a given low weight is more mature than a white infant of equal birth weight. Another factor in the decision, so far as length of stay in the hospital is concerned, would be the home conditions to which the infant would return. (See p. 113.)

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Data in regard to the influence of economic status on birth weight are meager. In an unpublished Children's Bureau study of infants born over a period of several years 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 4,704 white single-born infants, of whom 258 weighed less than 2,500 gm. The incidence of prematurity was higher among the 2,192 ward patients (6.8 percent) than among the 2,512 private and semiprivate patients (4.3 percent).

Confirmation of the probable role of economic factors in the incidence of premature birth is found in a more recent study by Eastman (35), who analyzed incidence by economic status and race and by extent of prenatal care, and discussed maternal dietary deficiency as an underlying cause. Unfortunately Eastman's figures are not comparable with those already given because in this part of his discussion his figures for "premature infants" include stillbirths, which constituted 11.7 percent of his total premature group.

Among 2,457 single premature births (1926-45) in which onset of labor was spontaneous, Eastman (35, pp. 346-348) found that in the three weight groups studied (1,000-1,499 gm., 1,500-1,999 gm., and 2,000-2,499 gm.) the incidence of prematurity was greater (1) among white ward patients than among private patients and (2) among Negro ward patients than among white ward patients. In the weight group 2,000 to 2,499 gm. the figures for Negroes, he considers, might have been affected by the inclusion of a small number of mature infants, if the maturity weight of 2,350 gm., instead of 2,500 gm., is the one that should be accepted for Negro infants. To exclude the possible factor of a greater incidence of maternal disease in the lower economic groups he shows that differences in incidence of prematurity are found between private patients and white and Negro ward patients among 855 mothers (1936-45) for whom the pregnancy was single, labor spontaneous, and the premature birth "without demonstrable cause." He further tests the influence of economic and social factors by considering the effect on the incidence of prematurity of prenatal care, classified as none (no visits), poor (1 to 2 visits), and adequate (3 or more visits). Though the standard for "adequate" care is low, the incidence of premature birth in the 2,270 cases (1926-45) of single pregnancy with spontaneous onset of labor was 7.8 percent for women with good care, compared with 24.9 percent for women with poor care or none. When, in order to eliminate emergency cases and other cases of disease, analysis of the influence of prenatal care was limited to those "without demonstrable cause for premature birth," the figures (1936-45), although small for statistical analysis, still showed approximately the same results.

Eastman believes that the differences in incidence brought out by his study have an economic rather than a racial basis and, considering the studies of other investigators, that maternal dietary deficiencies are "a very probable explanation." (See pp. 28, 29.)

Summary

The incidence of premature birth in the United States is not known. For groups included in special studies based on gestation period it has been found to be approximately 5 percent of the total number of live

births. In studies based on a birth weight of 2,500 gm. or less the incidence is somewhat higher (7 to 11 percent).

When all infants weighing 2,500 gm. or less are regarded as premature the proportion of those of higher birth weight (2,000 gm. or more) is much greater than the proportion of those of lower birth weight (less than 2,000 gm.). In two large series the respective proportions for those of higher birth weight were 69 and 71 percent and for those of lower birth weight, 31 and 29 percent.

The incidence of prematurity has been found to vary with race, plurality of birth, and economic status, being higher among Negro infants, among plural-born infants, among those in the lower economic groups, and among those with inadequate prenatal care.

CAUSES AND PREVENTION OF PREMATURE BIRTH

The prevention of premature birth involves detection and correction of abnormal conditions in the mother before and during pregnancy.

Prenatal care by a physician should be given early in pregnancy and continued at regular intervals throughout pregnancy (101). Consideration should also 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 the 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. (Naegele's rule (29, p. 129) is to count back 3 months from, and add 7 days to, the date of the first day of the last menstruation.)

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 physician will also undertake specific measures, such as the treatment of diseases and disorders, with a view to bringing the pregnancy to term with mother and fetus in the best possible condition.

Premature birth may occur spontaneously without known cause or as the result of some abnormal maternal or fetal condition; or it may be brought about by premature induction of labor or operative termination of pregnancy for the welfare of the mother. The extent to which the expectant mother's physical condition determines whether or not her infant will be born prematurely is shown in figures reported by Parmelee (69, p. 252) from a study of 9,365 consecutive births at the Presbyterian Hospital in Chicago. Of the infants of the 6,007 mothers considered healthy, 5.2 percent were premature; of the infants of the 3,358 mothers who had some medical complications, 8.4 percent were premature.

The physician must be familiar with the known causes of premature labor in order to attempt to prevent the associated maternal disorders and to prolong pregnancy to the extent compatible with the welfare of mother and infant.

Specific conditions associated with premature birth

Table 5, adapted from a review of the literature on this subject by Anderson and Lyon (4), gives the lowest and the highest incidence of various conditions associated with premature birth reported by 13 American authors.

TABLE 5	Percentage incidence of various factors that may influence pre-	maturit y
	(13 American authors, according to Anderson and Lyon)	•

Conditions associated with premature birth	Lowest	Highest
No cause suggested	30.7	64.7
Multiple births	6.3 5.2	22. 9 29. 9
Bleeding: Placenta previa	1.5	4.4
Premature separation of placenta	1.3	5.1
Premature rupture of membranes	.4	20.9
Syphilis Serious illness of mother:	1.4	19.0
Heart disease	.5	2.6 3.9
Other acute and chronic conditions.	1.4	16.3
Pelvic deformities	.9	7.8
Myoma Hydramnios	.1	2.9
Trauma to mother Other conditions	.4 1.1	5.2 5.2

Anderson and associates (5) also studied the incidence of these conditions in mothers of mature as well as premature infants and found that though these conditions may be associated with delivery at term they appear with greater frequency among women who give birth to infants of low birth weight. Obviously, however, the period of pregnancy in which the condition occurs and its severity are important in respect to premature birth. The onset of labor may be spontaneous when one or more of these conditions are present, or the pregnancy may be terminated prematurely in the interest of mother and infant.

Apparently there is general agreement in regard to the chief causes of premature birth, although there is considerable variation in their reported incidence.

The various factors that may influence prematurity, shown in table 5, will now be discussed, as well as methods for reducing their incidence. Details of obstetric procedures in relation to these conditions are outside the scope of this book.

NO CAUSE REPORTED

In by far the largest proportion of cases (30.7 to 64.7 percent) no cause of the premature birth was reported. The proportion of these cases will obviously be lowered by more detailed information and, as many of these infants die, by careful antemortem and postmortem examinations. Potter (75, p. 528) states:

"There is a remarkably close correlation between the clinical course of infants during the newborn period and the findings present on postmortem examination. The pathologist can be of immeasurable help

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to the clinician in reconstructing the course of events leading to death in the newborn period or during the course of labor.

"To be able to combat a disease the disease must be known. The frequently repeated statement that the majority of infants die for unknown reasons is untrue. Rarely is there an infant for whom a cause of death cannot be found by combined study of clinical and pathologic data.

"The particular fields yet to be conquered in the prevention of death in this age period center about premature delivery, antepartum intrauterine death, and malformations."

MULTIPLE BIRTHS

Multiple births were reported to be responsible for 6.3 to 22.9 percent of premature births. When the diagnosis of multiple births is made special precautions should be taken to prevent premature onset of labor. It should be pointed out, however, that small plural-born infants are often more mature than single-born infants of the same birth weight.

TOXEMIA OF PREGNANCY

Toxemia of pregnancy accounted for a very wide range (5.2 to 29.9 percent) of the premature births reported. This wide variation may be the result of differences in the incidence of toxemia in different areas of the United States or of differences in classification and diagnosis.

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 prenatal care is given, with proper regard to the mother's diet and rest, severe toxemia and eclampsia, with which premature birth is most frequently associated, usually do not 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 (about 1,500 gm.).

ANTEPARTUM HEMORRHAGE

Antepartum hemorrhage also is frequently associated with premature birth. The hemorrhage may be caused by **premature separation** of the normally implanted placenta; prevention or control of toxemia will tend to prevent this condition. On the other hand, the hemorrhage may be caused by **placenta previa**, which appears to be an unavoidable complication of pregnancy. When hemorrhage from this cause occurs the chances for mother and infant are greatly increased by hospitalization.

Beck (10, p. 358) has suggested that whenever abdominal pain and vaginal bleeding indicate the imminence of premature labor, the immediate steps to prolong the pregnancy should include rest in bed, "large doses" of progesterone, and treatment of the underlying cause of the uterine irritability. Falls and associates (37, p. 298) believe that "the prolongation of gestation by means of these injections [corpusluteum extracts] when the fetus is on the borderline of viability and premature delivery seems imminent is desirable and not unreasonably dangerous."

It seems necessary at this point to discuss the prevention of abortion because some infants born as the result of late "abortions" survive. even though they may be "nonviable" according to criteria in general (See p. 3.) Bleeding that occurs before the twenty-eighth week use. of pregnancy usually is not classified as due to either placenta previa or premature separation of the placenta but is usually referred to as threatened abortion. When abortion occurs in successive pregnancies the condition is referred to as *habitual abortion*. Threatened abortion, according to Hertig and Livingstone (47, p. 805), occurs in at least 16 percent of all pregnancies. Habitual abortion, they estimate, occurs in about 4 percent of all spontaneous abortions, or about 0.4 percent of all pregnancies. A certain number of such abortions are caused by endometritis, uterine displacement, or defective germ plasm; in other cases a vitamin or hormone deficiency may be responsible. (For discussion of abortion in relation to the Rh factor, see p. 286.)

Treatment of both threatened and habitual abortion with hormones and with vitamin E, separately or in combination, and with thyroid extract has been advocated, in connection with emphasis on bed rest and the importance of adequate maternal diet and supplementation with vitamins C and K. Shute and Shute (92) appear to be in the minority in believing that vitamin E alone is effective. Falls and his coworkers (37) claim satisfactory results from the use

Falls and his coworkers (37) claim satisfactory results from the use of corpus-luteum extracts in approximately 85 percent of 650 cases including both threatened and habitual abortions.

Hertig and Livingstone (47), while recognizing the need for further study of causes and evaluation of various therapeutic agents, believe that for the present the treatment of both threatened and habitual abortion "rests upon the physician's practical judgment aided by empiric uses of more or less specific substances whose action is not fully understood at the present time." They state (p. 805):

"Threatened abortion should be treated by some potent corpusluteum preparation or, if estrogens are demonstrably low, by the administration of these substances. These hormones should be supplemented by vitamins E, C, and K and thyroid, in conjunction with a program of so-called nutritional adequacy. Habitual abortion should be treated in the same manner as is recommended for threatened abortion, except that treatment should begin prior to or coincident with conception."

Vaux and Rakoff (102) treated with large doses of estrogen and progesterone, in most cases until late in pregnancy, 35 women who had had 2 or more consecutive spontaneous abortions and who had shown estrogen-progesterone deficiencies both before and during pregnancy. The women also received mixed-vitamin capsules providing the minimum daily requirement. Of the 35 women 24 gave birth to living healthy infants and 9 had abortions or miscarriages. One full-term infant with multiple congenital abnormalities and one premature infant did not survive. These women had had 118 previous pregnancies, of which only 10 percent had resulted in full-term live births. The estrogen-progesterone ratio is the important factor in the treatment, according to these investigators.

Kurzrok (53) studied 280 selected cases of repeated miscarriage, in 42 of which he found evidence of genital hypoplasia. To remedy this condition Kurzrok gave estrogens throughout pregnancy, together with progesterone if necessary. Of the 42 women, 39 gave birth to normal infants, 2 of whom were born at the thirty-sixth to thirty-seventh week.

Hamblen (46) found that the results of antiabortional treatment with corpus-luteum extract in his clinic were not so satisfactory as those reported by others. Greenhill (45, p.52) believes that progesterone is usually unnecessary, sometimes has unfavorable results, and therefore should be given only after test has demonstrated deficiency. He uses estrogens alone in both threatened and habitual abortion and regards their use as a definite advance. Other measures that he uses include ruling out of focal infections before pregnancy, detection and treatment of syphilis, administration of thyroid extract if needed, and bed rest during the menses periods and the periods at which previous abortions occurred. He says (p.53), "Vitamin E may be given, although I have little faith in it."

Stander (95, pp. 737-743), in discussing habitual abortion, stresses the importance of adequate diet and considers progesterone and vitamin E in the form of wheat germ or wheat-germ oil of value in certain cases. He also cites reports of the successful use of thyroid extract. For threatened abortion, in addition to bed rest and sedation, he considers progesterone and vitamin E advisable, though he adds: "It should be noted, however, that our knowledge with regard to both the role and the dosage of these substances in the production and treatment, respectively, of threatened abortion is still incomplete, and we must await further reports on large series of cases before we can speak with any assurance about them."

Stander (95, p. 743) believes that in some circumstances abortion is desirable, and efforts to prevent it are sometimes continued unnecessarily long. He says: "In view of the part played by developmental abnormalities of the fetus in the production of abortion, it is apparent that in many instances its occurrence should not be regarded as a misfortune but rather as a conservative effort on the part of nature to rid the organism of a product of conception which cannot attain maturity." Schneider (88) calls attention to the fact that the reports on the prolongation of pregnancy through the prevention of abortion do not show increased incidence of malformed infants. Some evidence of increased risk, however, has been presented. (See Hertig and Livingstone, 47, p. 800.)

PREMATURE RUPTURE OF THE MEMBRANES

Premature rupture of the membranes plays a relatively important role in premature onset of labor, its reported incidence varying from less than 1 to 21 percent (table 5). The cause of the rupture is usually not reported. It has been suggested that chronic cervicitis and trauma of intercourse may be important factors. DeLee and Greenhill (29, p. 595) state that "the cause of premature rupture of the membranes is unknown but most likely there is some abnormality in the membranes which is responsible for the untimely rupture. The following may be responsible: abnormal presentation, contracted pelvis, low insertion of the placenta, multiple pregnancy, and polyhydramnios."

SYPHILIS

Maternal syphilis, of which the lowest reported incidence (table 5) was more than 1 percent and the highest was 19 percent, varies greatly

in different areas in the United States, as does the number of cases in which adequate prenatal treatment is given. Syphilis is the one cause of premature birth of which the possibility of prevention is definitely assured. It is well established that if treatment of the mother is begun early, at least before the fifth month of pregnancy, and is carried out adequately, syphilitic infection of the infant is prevented in a very large proportion of cases, and the incidence of premature birth is decreased.

Treatment with arsenicals

The results when arsenicals (plus, in some cases, mercury or bismuth) are given before and during pregnancy compared with results when no treatment is given are shown in table 6, in which Moore (66, p. 493) quotes findings of McKelvey and Turner on 943 cases at the Johns Hopkins Hospital from 1914 to 1930 (59).

	Number	Conditio at b	n of child birth	Ultimate	status of cl	uild known
Treatment of the mother	pregnan- cies	Percent living	Percent dead	Number of children	Percent normal	Percent syphilitic
None	268 82 391 202	54. 1 81. 7 90. 0 93. 1	45. 9 18. 3 10. 0 6. 9	155 46 260 135	35. 4 91. 3 81. 5 95. 5	64.5 8.6 18.4 4.5

 TABLE 6
 Influence of the time of antisyphilitic treatment upon the outcome of pregnancy (McKelvey and Turner as reported by Moore)

These results are confirmed by the findings of Benensohn (12) in a study at the Cook County [Ill.] Hospital of 935 syphilitic pregnancies in 789 of which therapy with arsenicals and bismuth was given. For the infants of mothers who received any treatment he reported "93.3 percent salvage"; "salvaged cases" included all infants followed for at least 6 weeks who did not present evidence of congenital syphilis. Among the 350 women who received adequate therapy (more than 10 treatments) all but 15 pregnancies terminated satisfactorily. Among the 113 women who had received adequate therapy during the current pregnancy and had also been treated previously there was an unsatisfactory outcome in only 1 case. Among the 146 mothers who received no treatment the outcome was satisfactory in only 61 percent.

Treatment with penicillin

Recent reports of treatment of syphilis with penicillin give hope for an even better prognosis for prevention of fetal syphilitic infection and thus of premature birth. Goodwin and Moore (43) report the results of their own studies and review those of Ingraham and his coworkers (50). Because of "the practical certainty of infection of a fetus born of a mother with outspoken early syphilis," the clinical material that formed the basis for these reports was limited to cases of primary and secondary syphilis occurring early in pregnancy.

To 57 pregnant women with early syphilis treated with penicillin in the two clinics (Baltimore and Philadelphia) 60 infants were born alive. All but 1 (the infant of a mother with a clinical relapse at the time of delivery) were free from clinical and laboratory evidences of congenital syphilis, and 42 of the 59 normal infants had been followed for a long enough time after birth "to make practically certain of the diagnosis of no syphilis."

Goodwin and Moore recommend that "in syphilitic pregnant women penicillin be used routinely for the prevention of prenatal syphilis, other methods of treatment being abandoned."

The results of treatment reported from their clinic (Baltimore) and that of Ingraham and associates (Philadelphia) are shown in table 7.

Recommendations in regard to treatment outlined by Goodwin and Moore are as follows (pp. 693-694):

"The data so far presented should be considered in conjunction with the known dangers of arsenic and bismuth therapy, the known nearly complete lack of toxicity of penicillin for the mother, and the compression of penicillin treatment within a minimum time period of a few days.

"In view of these facts, we are prepared to recommend that, for the purpose of prevention of prenatal syphilis, metal chemotherapy for the syphilitic mother whether with early or late (including latent) syphilis be abandoned and that penicillin be adopted universally in its stead.

"Since therapy for the fetus should be planned in conjunction with that for the mother herself, and since definitive information as to the optimum method of use of penicillin in early or late acquired syphilis of adults is not yet available, it is possible to recommend treatment plans at present only as preliminary information permits. Certain minimum requirements should be met:

- "1. The total dose of penicillin should be not less than 2.4 million units administered intramuscularly in aqueous or saline solution at intervals of not less than 2 nor more than 3 hours night and day.
- "2. The total duration of treatment should be not less than $7\frac{1}{2}$ days.
- **"3.** For the present and until definitive information is available from research centers, absorption-delaying methods of use of penicillin (i. e., as in peanut-oil and beeswax) should not be used.
- "4. Following completion of penicillin treatment, the mother must be followed clinically and with quantitatively titered serologic tests at least as often as once a month until delivery (and preferably for the first year after treatment) and at appropriate intervals thereafter.
- **"5.** Retreatment with penicillin should be given during pregnancy to the mother if (a) there is evidence of clinical or serologic relapse, or (b) the original maternal serologic titer does not significantly decline within 3 months after treatment.
- "6. The infant must be followed after birth for a minimum period of 3 months by means of (a) frequently repeated physical inspections, (b) quantitatively titered blood serologic tests, preferably every 2 weeks, and (c) roentgenograms of the long bones taken preferably at the first and sixth weeks of life.

TABLE 7 Status	of infaı	nts borı	n of penic	sillin-tr	eated n	others	as of S	ept. l	0, 194	5 (Ge	iwbo	n and	Moore	Ingral	nam et al.)
Author	Num- ber of moth- ers so	Num- ber of infants	Infants born alive ap-	In- fants devel- oping	Infants birth taneo duri mont	seropos revertiu usiy to r ng spe h of life	itive at g spon- legative ccified	Durat of in norr (mon	ion of ifants s nal s nths)	follow upparei ut b	-up ntly irth	Follow-1 appare birth	ip of ently noi	infants mal at	Death of infants apparently normal
	livered		at birth	ilis	lst	2d	3d	2	2-6	3-12	12+	Р. Б.	Х-гау	Sero- logic	·
Ingraham and others	*	1 27	22	-	2	7		~~~~	=	9	1	26 bormal	26 normal	26 Dormal	1 at 7 mo. of age from acute febrile lilness, undetermined cause, autopsy
Goodwin and Moore	31	:33	8	0	80		1	ø	18	~		33 lormal	• All normal	33 normal	negative for syphilis. 1 at 19 weeks, acute nutritional dis- turbance and slekte-cell anemia; STS negative at time; no autopsy.
Total	19	8	8	-	15	5	-	=	8	13	~	59 Jormal	4 All normal	59 normal	
¹ 1 mother had 2 pregn ² Mother given 1.2 mi elinical relapse in mothe	ancies du llion unit	tring the states for second	second of w ondary syp of pregnanc	hich no bilis at y; infan	freatmen fifth moi t infected	t was giv th of p	en. egnancy;	sho	2 moth Roentg rtage of	ers hac enogra	1 2 preg ms doi	rnancies ie routir out all o	during i lely in B f them n	the secon altimore ormal.	d of which no treatment was given.

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Premature Infants

- **"7.** There is no satisfactory evidence that abortion, actual or threatened, is more frequent during penicillin treatment of the mother than during other forms of antisyphilitic treatment, or indeed more frequent than the expected incidence of spontaneous abortion in normal women. Unless and until such evidence is forthcoming, speculation is useless as to whether the phenomenon is due to therapeutic shock or to the direct oxytocic action of penicillin.
 - On the basis of the data presented in this paper, we see no reason for unusual caution in initiating the penicillin treatment of syphilitic pregnant women.
- **"8.** It is not yet determined whether a woman with early syphilis, treated with penicillin while nonpregnant or during an earlier pregnancy, may be permitted to go through a subsequent pregnancy without treatment. Although three women in the present series have delivered normal children in a second pregnancy in which no treatment was given, further experience must accumulate before the point can be decided. Pending further information, a pregnant syphilitic woman previously treated with penicillin, and whether or not this earlier treatment was apparently successful as to the mother's infection, should be retreated with penicillin in each succeeding pregnancy."

(For treatment of congenital syphilis in the infant see p. 244.)

CARDIAC DISEASE

Cardiac disease, intensified by pregnancy, often results in the premature onset or induction of labor. Beck (10, p. 358) has pointed out that "most of these patients begin their gestations with a cardiac reserve which is unequal to the strain of pregnancy." A careful history and physical examination before conception, he believes, would make it clear that in many instances pregnancy should not be risked, though it has also been demonstrated that with proper treatment many women with heart disease may be safely brought to term. He stresses the importance of obstetric and cardiologic consultation in these cases in order that both mother and child may have the benefit of the optimum time for delivery. "Under proper medical management the improvement which takes place after the eighth month, when the blood volume begins to fall, is often so great that spontaneous delivery at term may be awaited and all thoughts of terminating the pregnancy dismissed (p. 360)."

Carr and Hamilton (24) found that though heart failure may occur at any month of pregnancy, the incidence is rather low up to the sixth month, rises rapidly to reach a peak in the eighth month, and then rapidly diminishes.

DIABETES MELLITUS

Fetal and neonatal mortality is very high among the offspring of diabetic women. To report on this mortality in relation to diabetes in the mother, Miller, Hurwitz, and Kuder (63, pp. 272, 275) studied hospital records of all diabetic pregnant women admitted to the Boston
Lying-In Hospital from 1930, the New Haven Hospital from 1928, and the New York Hospital from 1933, to the time of writing (1943?). They based their conclusions on 137 diabetic mothers who were observed in the three hospitals through 159 pregnancies that resulted in 162 live births and stillbirths. The conclusions follow:

- "1. In pregnancies complicated by diabetes mellitus the fetal and neonatal mortality [neonatal mortality is based on the first 10 days only] is about five times higher than that in nondiabetic pregnancies. The fetal and neonatal mortality is as high during the 5 years immediately preceding the onset of diabetic symptoms as after the syndrome has become established. An increased fetal and neonatal mortality can be observed from 15 to 20 years before the clinical symptoms and signs of diabetes can be recognized.
- **"2.** Infants with a birth weight of 5 kg. or more are born to women before they become diabetic with the same high frequency as after diabetic symptoms have appeared. The incidence of infants whose birth weight is 5 kg. or more is about 80 times higher in pregnancies complicated by diabetes than in nondiabetic pregnancies.
- **"3.** The fetal and neonatal mortality is no higher among those infants who weigh 4.5 kg. or more at birth than among those who weigh between 2.5 and 4.5 kg.
- **"4.** In the presence of mild diabetes (not requiring insulin) and in the absence of maternal complications of pregnancy the fetal and neonatal mortality is four times higher than that in the nondiabetic population. Severe complications of pregnancy in women with diabetes increase the risk to the infant.
- **"5.** The presence of glycosuria in the last months of pregnancy in women whose carbohydrate metabolism is otherwise apparently normal is associated with a fetal and neonatal mortality that is as high as that among the offspring of women with definite diabetic signs and symptoms."

In a study from January 1936 to June 1944 of 181 consecutive diabetic pregnancies at the George F. Baker Clinic of the New England Deaconess Hospital, White (104) found the diabetes associated with "high incidence of early, spontaneous, interrupted pregnancies, pre-eclamptic toxemia, uterine inertia, and failure of lactation." She considered imbalance of the sex hormones of pregnancy the most important single factor in bringing about these conditions. This imbalance "may also be responsible for production of the abnormal fetus, contributing to fetal edema, splanchnomegaly, and excessive hemopoiesis. The fetal survival and the clinical course have undergone a profound change with substitutional estrogen and progesterone therapy."

Table 8 shows the relation found in this study between hormonal balance and the incidence of prematurity, toxemia, and fetal survival. White comments (p. 181):

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"Fetal abnormalities are physical, chemical, and pathologic. A birth weight above the average for the period of gestation has been found in 80 percent of the infants of diabetic mothers. The size of

Hormonal balance		Percentage of premature deliveries	Percentage of toxemia	Percentage of fetal survival	
Total	181	16		84	
Normal Abnormal: Treated Not treated	52 91 38	0 15 40	2 (¹) 50	96 90 50	

 TABLE 8
 Percentage of premature deliveries, toxemia, and fetal survival according to hormonal balance (tabulated from White's figures)

¹ "It is difficult to measure the effect of hormonal correction on the incidence of toxemia in this series of **cases**, for the early ones were treated only after symptoms of toxemia had developed. In the past few years the therapy has been inaugurated on chemical evidence only, and the incidence of toxemia . . . has fallen to 5 percent."

the infant appears to be due to three distinct factors: obesity, edema, and splanchnomegaly, the liver, spleen, and heart being especially involved. The second physical abnormality is the high incidence of congenital defects, usually involving tissue which is mesenchymatous in origin."

The rules for the management of the pregnant diabetic patient in the George F. Baker Clinic are reported by White as follows (pp. 181-182):

"This management is diabetic, obstetric, endocrine, and pediatric. The diabetic diet should be liberal in calories, 30 per kg. of actual body weight; high in protein, 2 gm. per kg. of body weight; and adequate in carbohydrate, up to 200 gm. daily, 150 for the mother and 50 for the fetus. Because of the low renal threshold multiple small doses rather than a single large dose of insulin have been employed. Sodiumchloride intake is restricted and in abnormal cases ammonium chloride is administered.

"The delivery in the abnormal cases is premature, the time of choice being the latter part of the thirty-seventh or the early part of the thirtyeighth week. Cesarean section for this particular group is my personal choice. The anesthesia is spinal and sedation is prohibited.

"Various forms of endocrine therapy and various routes of administration have been used in this series of 181 cases. The best and most economical to date is diethylstilbestrol intramuscularly and progesterone intramuscularly. The average daily dose of each is 15 mg."

Smith, Smith, and Hurwitz (93) believe from a study of 16 pregnant diabetic women that there is a relationship between hormonal abnormalities and the accidents of late pregnancy that are common in diabetic women and frequently involve loss of the offspring. For technical reasons, however, studies of hormones, the authors say, would be of little assistance in determining which patients to treat. They therefore advocate administration of hormones to alternate diabetic patients for a sufficient period to yield statistically significant results.

THYROID DISEASE

Hyperthyroidism in the mother tends to increase the incidence of premature labor. Javert (51) found only 18 cases of "hyperthyroidism complicated by pregnancy" in the Woman's Clinic of the New York Hospital among the 23,439 pregnant women attending the clinic over a period of 7 years. Of these 18 women, 5 had abortions

(of which 4 were therapeutic done on account of the hyperthyroidism) and 10 of the remaining 13 had toxemia of pregnancy. Stander (95, p. 528) states: "Formerly the induction of premature labor was recommended whenever the symptoms became urgent, but with increasing surgical knowledge prompt operation upon the thyroid seems preferable." Mussey and Plummer (67) showed that "the operation of partial thyroidectomy in cases of adenomatous goiter with hyperthyroidism and . . . the use of . . . iodine in cases of exophthalmic goiter followed by partial thyroidectomy when . . . indicated enable the pregnant woman to carry through pregnancy with reasonable expectancy of health and of normal living offspring." In 28 cases of Graves disease and 10 cases of adenomatous goiter with hyperthyroidism associated with pregnancy which were observed in the Mayo Clinic from 1923 to 1930, there was no maternal death, no miscarriage, and only one premature delivery and one stillbirth. Stander (p. 528) states: "In general our treatment is in agreement with that of Mussey and his associates. Therapeutic abortion is rarely indicated, as women with hyperthyroidism may be followed safely during pregnancy . . ."

According to Stander (95, p. 528), "hypothyroidism . . ., whether associated with colloid goiter or not, often results in miscarriage as well as in cretinism or congenital goiter in the child." Litzenberg and Carey (55) found that if pregnant women with hypothyroidism were given thyroid medication the tendency to interruption of pregnancy was reduced.

ACUTE INFECTIOUS DISEASES AND TUBERCULOSIS

The pregnant woman should as far as possible avoid exposure to acute *infectious diseases*. If exposed to measles, she should be given convalescent serum, globulin extract or immune-serum globulin with a view to preventing the disease or at least modifying it. To prevent measles in those exposed 10 cc. of convalescent serum, 4 cc. of placental globulin extract, or 1-5 cc. of immune-serum globulin should be injected intramuscularly within the first 4 to 5 days after the initial exposure. (See 3, p. 58.) Avoidance of exposure to virus diseases, especially rubella, in the early months of pregnancy is important. (See Congenital Malformations, p. 184.)

Douglas (31) has pointed out that a number of infectious conditions occurring in the course of pregnancy respond to the use of sulfonamides. He discusses their use in **postabortal and puerperal infec**tions, gonorrhea, urinary-tract infections, and pneumonia. Although he does not discuss the relation of treatment to prevention of premature birth, he cites two cases in which pregnant women with colon-bacillus pyelitis were treated with sulfanilamide and the infants, though born slightly before term, were normal. Parks has found that since the use of sulfadiazine in pneumonia complicating pregnancy, the incidence of premature labor resulting from associated anoxia and toxemia has been definitely reduced. (Personal communication from J. L. Parks, M. D., George Washington University Hospital, Washington, D. C.)

Early diagnosis and treatment of *tuberculosis* will tend to prevent premature interruption of pregnancy.

OTHER CAUSES

Genital-tract abnormalities

Vaginitis, cervical abnormalities (infection or tears), and intrauterine abnormalities, such as tumors, may give rise to uterine irritability resulting in premature labor. Preconceptional or prenatal diagnosis and appropriate treatment are indicated.

Trauma

Many cases of premature labor are ascribed by the patient to a fall or a blow. Physicians, however, tend to minimize this causal relationship, though a few premature births are ascribed to this cause. (See table 5.)

Parks has found in a large series of cases in which a routine question was asked, at the time of hospital admission, as to the time of the last intercourse, that there was close association between recent intercourse and the premature onset of labor. (Personal communication from J. L. Parks, M. D., George Washington University Hospital, Washington, D. C.) Beck (10) has stated, "Because coitus may bring on labor, abstinence from sexual relations in the last trimester is advisable. This precautionary measure is especially indicated in those women who have had a blood-stained vaginal discharge at any time during pregnancy, as well as in those who have shown evidence of the predisposing causes of prematurity."

Economic status and duration of pregnancy

The mother's economic status, the type and amount of work that she does, and her nutritional status have been found to be associated with premature labor. Obviously these factors are closely related to one another. (See p. 12.)

Data in regard to the effect of these factors are somewhat meager. Laurié is quoted by Stander (94, p. 259) as having shown that the duration of pregnancy depends upon the extent to which the patient can spare herself during the last 3 months of pregnancy. Laurié found that pregnancy "was 20 days longer in 1,550 women who lived comfortably in a hospital for several months prior to delivery than in the same number of women who entered at the onset of labor. Her figures, then, go to show that hard work in poorly nourished women predisposes to the premature ending of pregnancy."

The studies of Peller (72) tend to corroborate those of Laurié. He found in his study of women of poor economic status delivered at the Vienna General Hospital that the incidence of premature birth, as judged by gestation period and by weight and length of the infant, was lower among primiparae who were not ill but had received care for 1 to 8 weeks before delivery in a rest home attached to the hospital, than among those who entered the hospital within the last week of their pregnancy.

The importance of such prolongation of pregnancy is emphasized by Clifford (26), who says that because of the rapid gain in weight of the fetus in the last weeks, even a slight prolongation makes the outlook for the infant more favorable. He states: "Evidence has been obtained suggesting that the weekly gain of the fetus in utero is 4 oz. during the seventh lunar month, 6 oz. during the eighth, and from 8 to 12 oz.

per week during the ninth month." (See Physical Growth, p. 58.) Benton (13) points out that "in general, premature birth is an event which is correlated with unfavorable socio-economic circumstances. In view of the indubitable relationship between intellectual development and socio-economic status, it is necessary to keep this fact constantly in mind in the evaluation of the findings of various researchers . . . in this field."

Nutritional factors

RELATION TO PREMATURITY

In recent years a number of studies have been made of diet during pregnancy. The incidence of premature birth was found by Ebbs and associates (36) and by Burke and associates (21) to be higher among mothers who had poor diets than among those who had good diets. Burke and her coworkers (22) subsequently reported that among the 216 women whose diets were studied during pregnancy, only 10 percent consumed during the fourth through the ninth month the daily amount of protein (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; increases in birth weight and birth length were found with each increment of protein. No infants weighing less than 5 lb. at birth were included in this analysis.

A group of 750 expectant mothers on a scientifically controlled diet reported by Tyson (100) had no premature infants, whereas 37 premature infants were born to a similar group of mothers not on the (Tyson includes stillborn as well as live-born premature special diet. infants in his discussion of various aspects of the problem. This figure therefore may include some stillbirths.) 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."

DIETARY REQUIREMENTS IN PREGNANCY

Standards set by different authors for dietary requirements in pregnancy vary considerably. The earlier standards, those of the League of Nations, will not be given, since they have been supplanted by those of the Food and Nutrition Board of the National Research Council (68), first issued in 1941 at the time of the National Nutrition Conference and revised in 1945. They are shown in table 9.

The allowances given in table 9 for a healthy woman weighing 56 kg. (123 lb.) should be decreased or increased proportionately for smaller or larger women and may vary greatly for women not in good The values given in the table are for content of foods as eaten health. and do not allow for losses in storage, cooking, and serving. Because such losses, especially of the water-soluble vitamins, may be extensive, provision should be made for them in planning practical dietaries.

						v	itamin	B 1	Ascor-	
Woman of moderate weight	Calo- ries	Pro- tein (gm.)	Cal- cium (gm.)	Iron (mg.)	Vita- min A (I. U. ²)	Thia- mine (mg.4)	Ribo- flavin (mg.)	Niacin (nico- tinic acid) (mg.)	bic acid (Vita- min C) (mg. ³)	Vita- min D (I. U.)
Sedentary Moderately active Very active. Pregnant (latter half of pregnancy)	2, 100 2, 500 3, 000 7 2, 500	60 60 60 85	0.8 .8 .8 1.5	12 12 12 15	5, 000 5, 000 5, 000 6, 000	1.1 1.2 1.5 1.8	1.5 1.6 2.0 2.5	11 12 15 18	70 70 70 100	(6) (6) (9) 400-800

TABLE 9 Recommended daily allowances for a healthy woman weighing 56 kg. (123 lb.)¹ (National Research Council)

¹ Tentative goal toward which to aim in planning practical dietaries can be met by a good diet with a variety of natural foods. Such a diet will also provide other minerals and vitamins, the requirements for which are less well known.

³ The allowance depends on the relative amounts of vitamin A and carotene. The allowances of the table are based on the premise that approximately two-thirds of the vitamin-A value of the average diet in this country is contributed by carotene and that carotene has half or less than half the value of vitamin A. ³ Foods supplying adequate thiamine, riboflavin, and niacin will tend to supply sufficient of the remain-ing B vitamins.

1 mg. thiamine=333 international units.
 1 mg. ascorbic acid=20 international units.

• For persons who have no opportunity for exposure to clear sunlight and for elderly persons the ingestion of small amounts of vitamin D may be desirable. Other adults probably have little need for vitamin D. ¹ During the latter part of pregnancy the calorie allowance should increase approximately 20 percent over the preceding level. The value of 2,500 calories represents the allowance for pregnant sedentary women.

The National Research Council makes further recommendations as follows on elements in the diet not included in the table (68, p. 11):

Though little information is available concerning the human requirement for fat, several factors make it desirable that fat be included in the diet to the extent of at least 20 to 25 percent of the total calories and that the fat intake include "essential" unsaturated fatty acids to the extent of at least 1 percent of the total calories. Since other foodstuffs contain "invisible" fat, only one-third to one-half of the total calories derived from fat need be supplied by butter, margarine, lard, and shortenings.

The daily requirement for *iodine*, especially important in pregnancy, is given as 0.15 to 0.30 mg., a need met by the regular use of iodized salt; for copper it is stated to be 1.0 to 2.0 mg., supplied normally if the diet is good. **Phosphorus** allowances should be at least equal to those for calcium in the diet of women during the latter part of pregnancy. In general, the Council believes, it is safe to assume that if the calcium and protein needs are met through common foods the phosphorus requirement also will be covered.

The needs for salt and for water are closely interrelated. A liberal allowance of sodium chloride for the adult is 5 gm. daily. The average normal intake of salt is 10 to 15 gm. daily, which meets the salt requirement for a water intake up to 4 liters daily. A suitable allowance of water for most adults is 2.5 liters daily, but water should be allowed ad libitum.

(For vitamin K requirement see p. 297.)

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Outline of conditions associated with prematurity

Conditions associated with premature birth, together with suggestions for prevention and treatment, may be outlined as follows:

Conditions	Prevention and Treatment							
Maternal toxemia	Adequate prenatal care. Regulation of diet.							
Antepartum hemorrhage:								
Placenta previa	Not known.							
Abruntio placentae (premature	Prevention of toxemia : hed rest at time							
separation of placenta).	of usual menstrual periods; hormone therapy.							
Acute and chronic diseases:								
Syphilis	Early diagnosis and adequate treatment before fifth month of pregnancy.							
Pyelitis	Early diagnosis and treatment.							
Pneumonia and other acute infec- tions.	Chemotherapy and antibiotics.							
Specific infectious diseases	Prevention of exposure; immunization.							
Cardiovascular-renal disease	Early diagnosis and treatment.							
Tuberculosis	Early diagnosis and treatment.							
Anemia	Early diagnosis and treatment.							
Endoctrine disturbances:	•							
Thyroid disease	Basal-metabolism test and treatment as indicated.							
Diabetes	Preconceptional diagnosis and treat- ment.							
Hormonal disturbance	Specific therapy.							
Genital-tract abnormalities	Early diagnosis and treatment appropri- ate to condition found.							
Hydramnios	Not known.							
Uterine abnormalities	Preconceptional diagnosis and treat- ment.							
Accidents	Warning to exercise caution.							
Sexual relations during pregnancy	Contraindicated after seventh month of pregnancy.							
Fetal abnormalities	Diet a possible factor; meeting protein needs important. Avoidance of virus infections, particularly, rubella							
Overwork and inadequate diet	Social and economic adjustments and education in nutrition.							

Summary

The incidence of premature birth, with its accompanying high mortality and morbidity, can be reduced by wider application of general measures to promote health and well-being in pregnancy and childbirth and of specific measures to combat abnormal maternal conditions associated with premature birth. In addition, further study is needed of these predisposing causes of premature labor, with a view to preventing premature birth or at least prolonging pregnancy until the infant reaches a weight compatible with a better chance of survival and development.

Prenatal care by a physician begun early in pregnancy and continued at regular intervals includes advice in regard to general hygiene and diet, as well as detection and correction of abnormal conditions.

Premature labor occurs spontaneously without known cause in 28 to 61 percent of pregnancies, according to studies reported. In addition, there are three important causes of premature labor for which no preventive measures are known: multiple births (6 to 23 percent), premature spontaneous rupture of the membranes (0.4 to 21 percent), and placenta previa (2 to 5 percent).

The known causes of premature labor include toxemia, antepartum hemorrhage, acute and chronic illnesses, genital-tract abnormalities, and occasionally trauma. Prevention of premature labor in these cases depends on early diagnosis and treatment appropriate to each case. Premature induction of labor is sometimes necessary for the mother's welfare, but it should be postponed as long as the mother's condition will permit, in order to give the infant the benefit of a longer period in utero, even if only a few days. There is some evidence that rest and adequate nutrition play a part in preventing prematurity.



DEATHS OF PREMATURE INFANTS IN THE UNITED STATES

The chief sources of information in regard to causes of death of premature infants are the National Office of Vital Statistics of the Public Health Service (until 1946, the Division of Vital Statistics of the Bureau of the Census), statistics compiled by individual hospitals on infants who were born and who died in the hospital; statistical studies of factors influencing mortality; and clinical and pathologic studies of causes of death among special groups of infants born alive and dying in the neonatal period.

The medical literature relating to causes of death of live-born premature infants has been confused by the methods used for reporting to the National Office of Vital Statistics. There has frequently been no clear distinction between a live birth and a stillbirth nor between causes of death determined in the infant and maternal conditions that affect fetal mortality but are not *immediate* causes of infant death. For example, maternal toxemia is an *underlying* cause of fetal death when it brings about premature labor and the birth of a very premature infant. A maternal toxic state may have some adverse effects on the infant, but it has not been shown to cause fetal toxemia. Antepartum hemorrhage (placenta previa or abruptio) may cause anoxia in the infant; anoxia is then the *immediate*, or primary, cause of infant death and antepartum hemorrhage, the *underlying* cause.

The rules of the National Office of Vital Statistics for certification of live births and stillbirths, and of causes of death of premature infants will be found in appendix 1 (p. 363).

National statistics

EXTENT OF PREMATURE-INFANT DEATHS

The figures of the National Office of Vital Statistics relating to premature infants show the deaths attributed to "premature birth," though deaths from other causes, among which are congenital malformations and birth injury, include those of some premature infants.

Premature birth takes a higher toll of infant life than any other condition, and it is one of the 10 leading causes of death among the general population. It was given as the cause of death in 1944 of 33,120 infants, of whom almost all (32,065), as would be expected, died during the first month of life. Deaths assigned to premature birth accounted for nearly oné-third (30 percent) of all the deaths during the first year of life and for almost half (46 percent) of those in the first month. (See tables 10 and 11 and fig. 1.) Many of the infants who died were doubtless too immature for survival, and their deaths were actually due to prematurity alone. Others, mature enough to survive, probably died from some undiagnosed condition or did not

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TABLE 10 Deaths in first year of life, by cause: Number of deaths, percentage distribution, and death rates; United States, 1944¹ (exclusive of stillbirths)

	Deaths i	Deaths in the first year of life					
Cause of death	Number	Percent distribu- tion	Deaths per 1,000 live births				
All causes	111, 127	100. 0	39.8				
Prenatal and natal causes	67, 713	60.9	24. 2				
Premature birth Congenital malformations Injury at birth. Congenital debility Other diseases peculiar to the first year of life Syphilis	33, 120 14, 205 10, 199 2, 493 6, 950 746	29.8 12.8 9.2 2.2 6.2 .7	11.8 5.1 3.6 .9 2.5 .3				
Influenza and pneumonia	15, 674 10, 230 2, 749 10, 340 4, 421	14. 1 9. 2 2. 5 9. 3 4. 0	5.6 3.7 1.0 3.7 1.6				

¹ Based on data from U. S. Bureau of the Census. Data are for continental United States.

Deaths in first month of life, by cause: Number of deaths, percentage distribution, and death rates; United States, 1944¹ (exclusive of TABLE 11 stillbirths)

	Deaths in	Deaths in the first month of life					
Cause of death	Number	Percent distri- bution	Deaths per 1,000 live births				
All causes	68, 996	100. 0	24.7				
Prenatal and natal causes	59, 349	86.0	21.3				
Premature birth. Congenital malformations. Injury at birth. Congenital debility Other diseases peculiar to the first year of life ²	32, 065 9, 195 9, 985 1, 303 6, 445 356	46.5 13.3 14.5 1.9 9.3 .5	11.5 3.3 3.6 .5 2.3 .1				
Influenza and pneumonia Dysentery, diarrhea, and enteritis All other specified causes Ill-defined and unknown causes	2, 902 1, 582 2, 594 2, 569	4. 2 2. 3 3. 8 3. 7	1.0 .6 .9 .9				

¹ Based on data from U. S. Bureau of the Census. Data are for continental United States. ² That occurred in the first month.

Saving these infants means increasing efforts receive proper care. to prevent premature birth; getting more detailed information on deaths assigned to premature birth alone; spreading knowledge of and facilities for the special care known to be needed by premature infants; and broadening through research the scope of knowledge in regard to problems of prematurity.

Deaths attributed to premature birth, as stated above, do not represent the entire loss of life associated with prematurity. All the other prenatal and natal causes (listed in tables 10 and 11) may include some deaths of premature infants. Prenatal and natal causes were responsible in 1944 for 67,713 (61 percent) of the deaths in the first year of life (111,127) and for 59,349 (86 percent) of the deaths in the first month

Deaths of Premature Infants



Figure 1.—Deaths in the first month of life, by cause, United States, 1944.

(68,996). Premature birth stood first in the prenatal and natal group, causing almost half of these deaths in the first year and more than half in the first month. Congenital malformations and injury at birth, to which premature infants are peculiarly liable, together accounted for 22 percent of the deaths in the first year and 28 percent of those in the first month. The number of deaths of premature infants in the cause group "other diseases peculiar to the first year of life" (asphyxia, nonsyphilitic infections, hemorrhagic disease, icterus gravis, and so forth) is limited by the fact that if premature birth is also mentioned on the death certificate it takes statistical precedence over these diseases. Causes outside the prenatal and natal group that would include some deaths of premature infants over 2 weeks of age are influenza and pneumonia and dysentery, diarrhea and enteritis. (If premature infants die of these causes in the first 2 weeks of life their deaths are assigned to "premature birth.")

It is obviously impossible to assess the total loss of infant life associated with prematurity from these figures, but studies of deaths of premature infants have demonstrated that the loss from the sources discussed, especially congenital malformations and birth injuries, would add considerably to the already high figures for "premature birth" alone.

DECREASE IN MORTALITY FROM PREMATURE BIRTH

That some progress has been made through the widespread recognition and study of the problem of prematurity in recent years is shown by the decrease from 1935 to 1944 in the neonatal mortality rate for premature birth. (See table 12 and fig. 2.) This rate showed a gradual decline from 14.9 deaths per 1,000 live births in 1935 to 11.5 in 1944, and the decline has been especially marked since 1937. During the 10-year period the decrease in the neonatal mortality rate for premature birth was 23 percent, compared with 24 percent in neonatal mortality from all causes and 29 percent in total infant mortality.

	Deaths pe bir	r 1.000 live ths	Percent change from preceding year		
I GAL	All causes	Premature birth	All causes	Premature birth	
1935	32. 4 32. 6 31. 3 29. 6 29. 3 28. 8 27. 7 25. 7 24. 7 24. 7	14.9 15.1 14.8 13.8 13.8 13.3 12.8 11.9 11.4 11.5	$ \begin{array}{r} +0.6 \\ -4.0 \\ -5.4 \\ -1.0 \\ -1.7 \\ -3.8 \\ -7.2 \\ -3.9 \\ 0 \\ \end{array} $	$ \begin{array}{r} +1.3 \\ -2.0 \\ -6.8 \\ 0 \\ -3.6 \\ -3.8 \\ -7.0 \\ -4.2 \\ +.9 \end{array} $	

 TABLE 12
 Deaths in first month of life from all causes and from premature birth; United States, 1935-44¹ (exclusive of stillbirths)

¹ Based on data from U. S. Bureau of the Census. Data are for continental United States.

The neonatal mortality rate for premature birth among Negro infants is higher than among white infants, and this relationship has been maintained consistently in the period 1935–44, the rate for Negro infants in 1944 (14.6) being the same as the rate for white infants in 1935. (See table 13 and fig. 3. The rates are for infants of nonwhite races. But since Negro infants comprise not less than 95 percent of these, the term Negro is used in this report for the entire group.) The neonatal mortality rate for Negro infants fluctuated irregularly from 1935 to 1941, when the rate was about the same as at the beginning of the period. But from 1941 to 1944 it dropped 14 percent, compared with 11 percent for white infants, in spite of a slight rise in 1944. This 14-percent decrease from 1941 to 1944 thus represents the entire decrease for Negro infants over the 10-year period 1935–44, while the 10-year decrease for white infants was 25 percent.



Figure 2.—Deaths in first month of life from all causes and from premature birth, United States, 1935–44.

Deaths of Premature Infants

Year	Number	of births	Deaths in of life from bin	first month premature rth	Deaths in first month of life from premature birth per 1,000 live births		
	White	Nonwhite	White	Nonwhite	White	Nonwhite	
1935	1, 888, 012	267, 093	27, 513	4, 508	14. 6	16. 9	
1936	1, 881, 883	262, 907	27, 786	4, 666	14. 8	17. 7	
1937	1, 928, 437	274, 900	27, 635	4, 889	14. 3	17. 8	
1938	2, 005, 955	281, 007	26, 905	4, 677	13. 4	16. 6	
1939	1, 982, 671	282, 917	26, 491	4, 769	13. 4	16. 9	
1940	2, 067, 953	292, 446	26, 620	4, 817	12.9	16.5	
1941	2, 204, 903	308, 524	27, 034	5, 244	12.3	17.0	
1942	2, 486, 934	322, 062	28, 588	4, 895	11.5	15.2	
1943	2, 594, 763	340, 097	28, 670	4, 843	11.0	14.2	
1944	2, 454, 700	340, 100	27, 109	4, 956	11.0	14.6	

 TABLE 13 Deaths in first month of life from premature birth, by race; United States, 1935-44 ¹ (exclusive of stillbirths)

¹ Based on data from U. S. Bureau of the Census. Data are for continental United States.

AGE AT DEATH

Almost all (97 percent) of the deaths attributed to premature birth in 1944 occurred in the first month of life. The first day was the most critical period, with 57 percent of the deaths; 29 percent occurred from the second to the seventh day; and 10 percent, from the second week to the first month. (See table 14 and fig. 4.)

VARIATIONS AMONG THE STATES

The States vary widely in neonatal mortality rates from premature birth. (See table 15.) They also vary widely in the degree of completeness with which they report births, and these differences obviously affect the comparability of their reported rates of death. Before a State is admitted to the United States birth-registration area a test by the United States Bureau of the Census must show that at least 90



Figure 3.—Deaths in first month of life from premature birth, by race, United States, 1935–44.

	Infants the	Infants that died from premature birth					
Age at death	Number Percent		Deaths per 1,000 live births				
Total	33, 120	100. 0	11.8				
Under 1 day 1 day to under 1 week 1 week to under 1 month 1 month to under 1 year	18, 909 9, 750 3, 406 1, 055	57. 1 29. 4 10. 3 3. 2	6.7 3.5 1.2 .4				

 TABLE 14 Deaths from premature birth, by age; United States, 1944¹ (exclusive of stillbirths)

¹ Based on data from U. S. Bureau of the Census. Data are for continental United States.

percent of its births are reported. All the States had been admitted to the area by 1933. In 1940, however, the Bureau of the Census (19, p. 5, table D; 54, 103) tested the completeness of birth registration throughout the country and found that 13 States had fallen below this standard since their admission; 12 States, on the other hand, were found to be registering 98 percent or more of the births.

Among the 35 States and the District of Columbia whose birth registration met the 1940 test of 90 percent completeness, the lowest rates for neonatal mortality from premature birth in 1944 were those of Mississippi (8.9), Illinois (9.2), and Kansas (9.3). The highest rates were those of Nevada (17.5) and the District of Columbia (17.6). Both Nevada and the District of Columbia had higher rates in 1944 than in 1943, as had 15 other States in the satisfactory birth-registration group, while the States with the lowest rates, Mississippi, Illinois, Kansas, and 15 other States showed some decline. One State was stationary. For the country as a whole the rate in 1944 was 11.5, compared with 11.4 in the preceding year, 1943. The 1943 figure showed a decline from 1942 (11.9). In the face of wartime shortages of medical and nursing services 1944 practically maintained the 1943 level.

Nineteen hundred and forty-three was the first year in which any State with satisfactory birth registration had a rate less than 9.0 for neonatal mortality from premature birth (Oregon, 8.2, and Connecti-



Figure 4.—Deaths from premature birth, by age, United States, 1944.

Deaths of Premature Infants

TABLE 15 Deaths in first month of life from premature birth for continental United States and for each State; 1935-44 ' (exclusive of stillbirths)

State	Deaths under 1 month from premature birth per 1,000 live births									
51816	1935	1936	1937	1938	1939	1940	1941	1942	1943	1944
Continental United States	14. 9	15. 1	14.8	13.8	13.8	13. 3	12.8	11.9	11.4	11. 5
States with birth registration 90 percent complete in 1940										
California Colorado. Connecticut Delaware District of Columbia. Florida. Idaho Illinois. Indiana Iowa. Kansas. Maine Maryland Massachusetts. Michigan Maryland Massachusetts. Michigan Mississippi Missouri. Mississippi Missouri. Montana. Nebraska Montana. Nebraska New Jersey. New Hampshire. New Jersey. New Hampshire. New Jersey. New York. North Dakota. Ohio Oregon. Pennsylvania. Rhode Island. South Dakota. Utah. Virginia. Wisconsin. Wyoming.	$\begin{array}{c} 14.8\\ 19.0\\ 12.7\\ 22.2\\ 22.16\\ 13.9\\ 13.9\\ 13.8\\ 4\\ 16.6\\ 6\\ 15.1\\ 13.9\\ 13.8\\ 4\\ 16.6\\ 6\\ 15.1\\ 13.9\\ 226.7\\ 13.0\\ 13.6\\ 4\\ 13.1\\ 13.6\\ 4\\ 13.1\\ 1$	$\begin{array}{c} 15.1\\ 17.4\\ 13.0\\ 23.7\\ 17.0\\ 12.9\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 14.7\\ 15.2\\ 11.4\\ 14.8\\ 10.4\\ 12.9\\ 14.5\\ 12.1\\ 13.4\\ 12.9\\ 14.5\\ 13.4\\ 12.7\\ 13.1\\ 11.7\\ 12.7\\ 13.1\\ 11.7\\ 11.7\\$	$\begin{array}{c} 15.3\\ 14.2\\ 17.2\\ 22.6\\ 17.8\\ 12.9\\ 12.4\\ 13.7\\ 13.3\\ 17.1\\ 13.5\\ 0.3\\ 17.1\\ 13.5\\ 13.2\\ 14.5\\ 13.6\\ 14.7\\ 11.8\\ 16.4\\ 14.3\\ 16.4\\ 13.6\\ 11.8\\ 11.8\\ 13.6\\ 11.8\\ $	$\begin{array}{c} 13.2 \\ 13.2 \\ 11.8 \\ 13.1 \\ 11.8 \\ 12.6 \\ 12.8 \\ 13.3 \\ 11.8 \\ 12.6 \\ 12.8 \\ 13.1 \\ 15.4 \\ 11.1 \\ 13.3 \\ 11.8 \\ 11.1 \\ 13.3 \\ 11.8 \\ 11.2 \\ 15.4 \\ 11.2 \\ 12.5 \\ 12.7 \\ 11.9 \\ 12.8 \\ 11.9 \\ 12.6 \\ 12.6 \\ 12$	$\begin{array}{c} 13.4 \\ 9 \\ 12.0 \\ 7 \\ 18.0 \\ 16.1 \\ 11.2 \\ 5 \\ 13.5 \\ 13.3 \\ 13.8 \\ 10.5 \\ 20.2 \\ 13.2 \\ 11.2 \\ 13.1 \\ 13.9 \\ 13.2 \\ 13.2 \\ 13.2 \\ 13.2 \\ 11.3 \\ 13.2 \\ 11.3 \\ 13.2 \\ 11.3 \\ 13.2 \\ 11.3 \\ 11.3 \\ 11.4 \\ 14.5 \\ 12.2 \\ 12.0 \\ 21 \\ 11.7 \\ 11.7 \\ 11.7 \\ 11.2 \\ 11.7 \\ 11.2 \\ 11.7 \\ 11.2 \\ 11.2 \\ 11.7 \\ 11.2 \\ 11.2 \\ 11.7 \\ 11.2 \\ 11.7 \\ 11.2 \\ 11.7 \\$	$\begin{array}{c} 12.6\\ 17.8\\ 11.2\\ 14.1\\ 15.7\\ 13.1\\ 11.3\\ 11.9\\ 12.3\\ 11.5\\ 11.3\\ 11.5\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 12.4\\ 11.6\\ 13.2\\ 10.6\\ 13.2\\ 10.6\\ 13.9\\ 15.8\\ 15.8\\ 10.7\\ 10.7\\ 10.7\\ 10.7\\ 10.7\\ 10.7\\ 10.7\\ 10.6\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 15.8\\ 13.9\\ 13.5\\$	$\begin{array}{c} 12.8\\ 9.3\\ 11.9\\ 15.0\\ 11.4\\ 10.6\\ 8.11.9\\ 11.4\\ 10.6\\ 11.4\\ 11.8\\ 12.2\\ 12.7\\ 12.2\\ 12.7\\ 11.4\\ 12.2\\ 9.4\\ 12.4\\ 9.6\\ 11.5\\ $	$\begin{array}{c} 11.0\\ 9.4\\ 12.9\\ 9.4\\ 12.9\\ 15.4\\ 13.8\\ 10.9\\ 11.3\\ 11.2\\ 10.8\\ 10.9\\ 11.3\\ 11.3\\ 11.3\\ 11.6\\ 10.7\\ 12.2\\ 10.6\\ 10.7\\ 11.6\\ 10.6\\ 10.7\\ 12.9\\ 11.3\\ 11.6\\ 10.6\\ 10.7\\ 12.9\\ 11.3\\ 11.6\\ 10.6\\ 10.7\\ 12.9\\ 10.6\\ 10.7\\ 11.5\\ 10.6\\ 10.7\\ 10.6\\ 10.7\\ 1$	$\begin{array}{c} 10.9\\ 10.9\\ 10.7\\ 10.7\\ 10.2\\ 10.7\\ 10.2\\ 10.7\\ 10.2\\ 11.1\\ 10.7\\ 10.2\\ 11.1\\ 11.6\\$	11.6 $(3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3, 3$
90 percent in 1940 Alabama Arkansas Georgia Kentucky Louisiana New Mexico North Carolina Oklahoma South Carolina Tennessee Texas West Virginia	15.9 16.5 10.1 17.0 15.0 16.9 13.5 18.3 13.7 13.6 13.8 16.1 16.3	17.6 17.9 10.3 17.7 16.3 17.6 14.2 17.3 14.9 15.6 13.8 16.2 16.9	16. 4 17. 5 11. 7 16. 1 15. 3 16. 9 15. 5 18. 3 15. 2 15. 1 13. 9 15. 7 16. 5	14. 6 15. 6 10. 7 15. 6 16. 5 18. 2 13. 0 17. 2 13. 5 15. 1 12. 9 14. 2 15. 1	16. 3 17. 0 11. 1 15. 7 16. 3 15. 9 16. 0 16. 7 15. 0 15. 8 13. 7 15. 4 15. 0	15.8 14.5 9.1 14.8 15.4 16.8 14.7 15.8 15.4 14.2 12.4 15.5 15.0	15. 2 14. 8 10. 2 15. 1 14. 3 17. 0 14. 0 14. 5 15. 3 14. 9 15. 4 15. 2	12.9 15.2 9.3 14.1 12.9 12.8 15.4 13.7 12.0 14.4 11.9 14.1 15.6	10. 2 13. 1 7. 6 13. 1 12. 6 12. 5 15. 4 12. 5 13. 5 13. 5 13. 4 11. 2 13. 1 14. 3	11.7 8.3 12.7 11.9 14.0 15.5 11.8 12.9 14.0 11.7 12.3 13.8

¹ Based on data from U. S. Bureau of the Census.

cut, 8.7), and Mississippi was the only one of these States below 9.0 in 1944. But in 1944, of the 35 States and the District of Columbia with satisfactory birth registration, 10 States (Connecticut, Illinois, Indiana, Kansas, Mississippi, Montana, Oregon, South Dakota, Washington, and Wisconsin) had a rate of 10.0 or less, as against 9 States in 1943 and only 4 States in 1942. All the States with these low rates in 1944 stood 95 percent or higher in completeness of birth registration except Mississippi, for which the percentage of completeness was 90. Since the rates in some States are based on small numbers and there

is considerable fluctuation from year to year, the trend is seen more

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readily if the rates are calculated on the basis of all the births and all the deaths during 3-year periods. Table 16 shows, for 3-year periods and for the 11 States and the District of Columbia whose birth registration in 1940 was at least 98 percent complete, the infant mortality rates, the neonatal mortality rates, and the percentage decreases in the rates from 1933-35 to 1942-44.

TABLE 16 Deaths in first year of life and deaths from premature birth in first month of life in the 11 States and the District of Columbia with birth registration 98 percent complete in 1940: Deaths per 1,000 live births, 1933-35 to 1942-44¹ (exclusive of stillbirths)

	Deat	hs in fi	rst year c live birth	of life per 15	1,000	Deaths in first month of life from pre- mature birth per 1,000 live births				
State	By place of occurrence			Ву	Percent de-	By place of occurrence			By place of resi- dence, 1942-44	Percent de-
	1933-35 1936-38 1939-41 2 Place crease of resi- 1942-44 1942-44 1942-44 1942-44 1942-44	1 933 –35	1936–38	1939-41 ²	crease from 1933-35 to 1942-44					
California Connecticut District of Columbia. Massachusetts Michigan Minnesota Montana New Hampshire New Jersey. New York. Rhode Island Washington	51. 646. 763. 949. 750. 046. 555. 156. 947. 251. 252. 242. 5	$\begin{array}{r} 49.9\\ 39.5\\ 60.0\\ 43.5\\ 47.6\\ 41.3\\ 51.0\\ 47.3\\ 41.1\\ 44.2\\ 46.5\\ 41.2 \end{array}$	$\begin{array}{c} 39.3\\ 33.5\\ 48.6\\ 36.6\\ 40.4\\ 34.5\\ 44.1\\ 40.6\\ 36.8\\ 36.4\\ 37.8\\ 35.8\end{array}$	$\begin{array}{c} 34.\ 6\\ 29.\ 9\\ 47.\ 7\\ 33.\ 1\\ 37.\ 8\\ 30.\ 6\\ 36.\ 1\\ 40.\ 0\\ 32.\ 9\\ 32.\ 5\\ 39.\ 5\\ 34.\ 0\end{array}$	32. 9 36. 0 25. 4 33. 4 24. 4 34. 2 34. 5 29. 7 30. 3 36. 5 24. 3 20. 0	15. 1 13. 8 23. 0 14. 3 15. 8 15. 3 15. 7 17. 6 14. 0 14. 4 15. 0 12. 8	14. 5 13. 0 21. 2 13. 8 14. 6 13. 5 13. 9 14. 8 12. 2 13. 0 13. 3 12. 6	12. 9 10. 8 16. 8 11. 3 12. 8 12. 0 13. 8 12. 2 12. 2 12. 3 11. 4 10. 6 11. 1	11. 2 9. 3 16. 2 10. 5 12. 0 10. 6 10. 8 12. 3 10. 6 10. 6 10. 6 10. 4 9. 8	25. 8 32. 6 29. 6 26. 6 24. 1 30. 7 31. 2 30. 1 24. 3 26. 4 30. 7 23. 4

¹ Based on data from U. S. Bureau of the Census. ² Figures for 1939 and 1940 are by place of occurrence; figures for 1941 are by place of residence because they are not available by place of occurrence. Through 1938 practically all vital statistics were tabulated by the Bureau of the Census according to place of occurrence. However, the need and importance of residence statistics were keenly felt by all persons interested in vital statistics. Consequently, the staff of the Bureau decided to change to residence tabulations, though they realized that all statistics by States prior to and including 1938 would not be entirely comparable to those compiled for years following 1938. For the years 1939 and 1940 as many tabulations as possible were made by both occurrence and residence, but starting with 1941, nearly all information is given only on a residence basis. When rates by occurrence and by residence for the 11 States and the District of Columbia included in the table were compared for the years for which both were available, little difference was found except in the District of Columbia.

Infant mortality rates lower than that for continental United States (40.2) were reported for 10 of these 11 States in 1942-44, but the District of Columbia was higher (47.7) and New Hampshire (40.0) was practically the same. In neonatal mortality rates for premature birth all except the District of Columbia (16.2), Michigan (12.0), and New Hampshire (12.3) were below the national rate (11.6) by percentages ranging from 3.4 to 19.8. The total infant mortality rate for continental United States declined from 58.0 in 1933-35 to 40.2 in 1942-44; the neonatal mortality rate for premature birth, from 15.2 to 11.6.

For total infant mortality the decrease in rates from 1933-35 to 1942-44 varied from 20.0 percent for Washington to 36.5 percent for New York; for neonatal mortality from premature birth the decrease varied from 23.4 percent for Washington to 32.6 percent for Connecti-cut. Connecticut thus had both the lowest rate in this group in 1942-44 and the greatest relative decrease from 1933-35.

40

Hospital statistics

Hospital statistics in regard to deaths of premature infants are reported as fatality rates; that is, deaths per 100 premature infants born on the maternity service or per 100 premature infants admitted to the pediatric service. Data from different hospitals vary widely and unfortunately are frequently 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 as nonviable of infants of less than a specified period of gestation or weight, and (4) failure to tabulate data in comparable birth-weight groups by race and age at death.

The American Academy of Pediatrics has recommended that all infants born alive who weigh 2,500 gm. (5 lb. 8 oz.) or less, regardless of how short a time they live, be included in reports as premature and that the mortality be recorded in specified birth-weight groups.

FATALITY RATES TO 1940

Table 17 gives the fatality rates in 12 hospitals in the United States that were compiled according to the recommended birth-weight groups. Data given are for periods between 1922 and 1940, and for 8 of the hospitals the periods covered range from 6 to 18 years.

		Num-	Fatality rate (percent)					
Name of hospital	Dates	prema- ture in- fants 2,500 gm. or less	Total 2,500 gm. or less	Less than 1,000 gm.	lity rate (percent) $\begin{array}{c c} 3 \\ 1,000-\\ 1,500\\ 2,000\\ gm.^2\\ gm.^2\\ 5 \\ 50.0 \\ 21.6 \\ 0 \\ 62.2 \\ 21.8 \\ 0 \\ 72.9 \\ 17.4 \\ 0 \\ 69.2 \\ 31.0 \\ 3 \\ 54.1 \\ 22.3 \\ 0 \\ 75.5 \\ 34.3 \\ 0 \\ 73.0 \\ 31.8 \\ 0 \\ 66.3 \\ 41.1 \\ 1 $	2,001- 2,500 gm.		
Sarah Morris Hospital, Chicago Louisville City Hospital. New Haven Hospital. Chicago Lying-In Hospital 4. University of Illinois Hospital, Chicago Herman Kieler Hospital, Detroit. Boston Lying-In Hospital. Sloane Hospital for Women, New York City. Strong Memorial and Municipal Hospital, Rochester General Hospital. Long Island College Hospital. Brooklyn,	1922-39 1926-31 1924-33 (⁵) 1925-39 1939 1935-40 1929-34 (³) (⁶) 1924-39	3,883 3 538 244 655 717 246 1,005 330 400 587 1,106	27. 1 (3) 27. 0 19. 7 15. 9 19. 9 18. 0 25. 1 32. 0 26. 6 27. 2	87.5 (3) 100.0 90.0 100.0 90.3 100.0 100.0 100.0 95.0	50.0 82.5 62.2 70.6 72.9 69.2 54.1 66.0 75.5 73.0 66.3	21. 6 45. 6 21. 8 23. 8 17. 4 31. 0 23. 1 22. 3 34. 3 31. 8 41. 1	11.0 15.9 5.7 6.0 3.9 4.5 4.1 7.5 8.9 8.5 10.3	
Pediatric Department. Johns Hopkins Hospital, Baltimore, Ob- stetric Department.	1926-40	³ 2, 940	(8)	(3)	63. 2	24. 9	5.8	

 TABLE 17
 Fatality rates among premature infants by birth-weight groups; 1

 12 hospitals reporting 12,651 cases within the period from 1922 to 1940

¹ Some of the hospitals used the weight groups 1,000-1,499, 1,500-1,999, and 2,000-2,499 gm.
 ² The Academy of Pediatrics (2) suggested that infants weighing 1,000 to 1,500 gm. be studied in two groups: 1,000 to 1,250 gm. and 1,251 to 1,500 gm.
 ³ Infants weighing less than 1,000 gm. are not included. The total rate is therefore not comparable with

those of the other hospitals. 4 10,662 consecutive births

• Not given.

In addition, there were 19 premature infants not weighed at birth, all of whom died. When they are included the total fatality rate is 28.4 percent.

Except for four personal communications these figures were compiled from published sources. The total number of premature infants included in these studies was 12,651; in the individual studies the number ranged from 244 to 3,883. When the figures were analyzed for each hospital in the four birth-weight groups percentages were calculated in some instances on a relatively small number of cases. This was especially true in the lowest birth-weight group (less than 1,000 gm.); in the 9 hospitals for which the information was given rates were based on numbers varying from 11 to 77, and 6 of these hospitals had less than 50 cases, even though the studies covered considerable periods.

From the data presented it can be seen that (1) the fatality rate is inversely proportional to the birth weight, that is, the lower the birth weight, the higher the mortality; (2) the fatality rates in each birth-weight group vary considerably.

RECENT FATALITY RATES

Recent reports of hospital fatality rates compiled according to the recommendations of the American Academy of Pediatrics are shown in table 18 for six hospitals, four of which (the Boston Lying-In Hospital, Johns Hopkins Hospital, the Long Island College Hospital, and the Sarah Morris Hospital) were included in table 17. The figures given are for 2-year to 6-year periods between 1940 and 1945.

 TABLE 18
 Fatality rates among premature infants by birth-weight groups: 1

 6
 hospitals reporting 5,731 cases within the period from 1940 to 1945

		Num- ber of	Fatality rate (percent)					
Name of hospital	Dates	prema- ture infants 2,500 gm. or less	Total 2,500 gm. or less	Less than 1,000 gm.	1,000– 1,500 gm.²	1,501- 2,000 gm.	2,001- 2,500 gm.	
Sarah Morris Hospital, Chicago Boston Lying-In Hospital.	1940–45 1943–45	1, 993 481	25. 8 15. 0	91. 3 100. 0	50. 0 46. 7	14. 4 12. 8	7. 2 4. 4	
Startic Department	1941–45 1944–45 1943–45	3 994 1, 122 506	(3) 27.4 22.3	(*) 95. 7 85. 0	48, 8 55, 4 49, 3	16. 8 30. 5 21. 4	4.2 7.9 5.6	
Pediatric Department	1940-45	4 635	16.1	90.0	41. 4	18.3	4.6	

¹ Some of the hospitals used the weight groups 1,000-1,499, 1,500-1,999, and 2,000-2,499 gm.
 ³ The Academy of Pediatrics (2) suggested that infants weighing 1,000 to 1,500 gm. be studied in two groups: 1,000 to 1,250 gm. and 1,251 to 1,500 gm. are not included. The total rate is therefore not comparable with

those of the other hospitals. ⁴ In addition, there were 2 premature infants not weighed at birth, both of whom died. When they are included the total fatality rate is 16.3 percent.

One hospital (Boston Lying-In Hospital) included in both tables had relatively low rates even in the earlier period studied (1935-40). Yet in 1943-45 it showed marked decreases in the rates for the weight groups 1,000 to 1,500 gm. and 1,501 to 2,000 gm., and the total rate declined from 18.0 to 15.0. The Long Island College Hospital, which in the earlier period (1924-39) had fairly high rates, showed in the later period (1940-45) so striking a reduction in all weight groups except "less than 1,000 gm." that its total rate (16.1 percent) was almost as low as that of the Boston Lying-In Hospital (15.0 percent). In fact, for the period 1943-45, to which the Boston figures apply, the Long Island College Hospital rate was lower-13.6 percent. The Sarah Morris Hospital in Chicago reduced its total rate in the later period only 1.3 points; but in the weight groups 1,501 to 2,000 gm. and 2,001 to 2,500 gm. it reduced the fatality rate by one-third (1,501-2,000 gm.—21.6 to 14.4 percent; 2,001 to 2,500 gm.—11.0 to 7.2 percent). For Johns Hopkins Hospital a comparable total rate cannot be calculated because its figures do not include infants weighing less than 1,000 gm. at birth; but the percentages of fatality-rate reduction from the earlier to the later period in the three birth-weight groups from 1,000 gm. up were 23, 33, and 28, respectively.

Since with these four exceptions the hospitals listed in tables 17 and 18 are not the same and since the hospitals represented in both periods vary in type, comparisons of the rates in the earlier and the later periods are not conclusive. An additional factor affecting the comparability of these rates within as well as between periods is that full information with regard to the racial groups represented is not available. It is of interest to note, however, that the later rates are generally lower and vary less widely within the birth-weight groups, as is shown in table 19. This table also gives 1945 figures for New York City hospitals. (Personal communication from L. Baumgartner, M. D., Department of Health, City of New York, Feb. 7, 1947.)

	Fatality rate (percent)						
Period	Total 2,500	Less than	1,000–1,500	1,501-2,000	2,001-2, 590		
	gm. or less	1,000 gm.	gm.	gm.	gm.		
Earlier period (12 hospitals, 1922-40)	15. 9–32. 0	87. 5–100. 0	50. 0-82. 5	17. 4–45. 6	3. 9–15, 9		
Later period (6 hospitals, 1940-45)	15. 0–27. 4	85. 0–100. 0	41. 4-55. 4	12. 8–30. 5	4. 2– 7. 9		
New York City hospitals, 1945	17. 1	96. 1	62. 1	22. 9	6. 3		

TABLE 19 Range in hospital fatality rates in earlier and later periods

Tyson (100) has reported on a 15-year study of premature-infant mortality at the Philadelphia Lying-In Hospital (1930-44). The total neonatal fatality rate for live-born infants weighing 5 lb. 8 oz. (2,500 gm.) or less during the 15-year period, as calculated from Tyson's figures, was 25.3 and the trend was generally downward from 35 in 1930 to approximately 15 in 1941, after which it rose to approximately 24 (figures for individual years are approximate, taken from the author's chart 6, p. 653). The rates given by birth-weight groups are not comparable with those of other hospitals discussed because the group limits are given in pounds (under 2, 2-3, and so forth) and because these figures are not given separately for stillbirths and neonatal deaths.

COMPILING HOSPITAL STATISTICS

It is obvious that further studies offering more nearly complete information are needed for comparisons between hospitals and between periods. Moreover, for its own enlightenment as to progress in the care of premature infants, every hospital needs to analyze its own records in successive periods; and these periods should be longer than 1 year or conclusions may be misleading since the numbers in each weight group may be too small to be statistically significant.

Uniformity in methods of compiling hospital fatality rates is obviously important if comparisons between hospitals are to be made. It is suggested that the following plan be used:

- 1. Include in statistics all live-born infants weighing 2,500 gm. (5 lb. 8 oz.) or less, regardless of gestation period. No exclusions should be made on the basis of "nonviability." Arbitrary exclusions should not be made on the basis of low birth weight or birth length, gestation period, or duration of life.
- 2. Compile data for the total number of premature infants who are born alive and the total who die according to the birth-weight groups recommended in the resolution adopted by the American Academy of Pediatrics (2).
- 3. Compile data (a) for infants born in the hospital separately from those admitted to the hospital after birth; (b) by race—white, Negro, other—for the totals and the birthweight groups.

A suggested form for recording this information may be found in appendix 8, page 389.

Factors influencing mortality

Among the factors associated with deaths of premature infants that have been studied are the birth weight, race, and sex of the infants; plurality of birth; the mother's age and parity, and the complications of pregnancy, labor, and delivery.

BIRTH WEIGHT

When a birth weight of 2,500 gm. (5 lb. 8 oz.) or less is taken as evidence of prematurity it has been found that the mortality is inversely proportional to the birth weight. (See p. 42.)

RACE AND SEX

Certain race and sex differences in mortality rates have been reported. When these rates are studied for single-born infants according to birth-weight groups, the differences in mortality rates have been found to be more closely related to birth weight than to race or sex. For example, Duffield and associates (32), in a study based on more than 100,000 live births in New York City, found "no uniform or consistent differences between the mortality rates of single-born white and singleborn colored infants of the same sex having the same weight at birth. It appears that the higher neopatal mortality rate of the total group of single-born colored males (39 per 1,000 live births) compared with that of single-born white males (24) can be accounted for by the larger percentage of small infants among the single-born colored . . . Similarly, the higher neonatal mortality rate of the total group of single-born colored females (29 per 1,000 live births) compared with that of single-born white females (18) can be accounted for by the larger percentage of smaller infants among the single-born colored.'

The findings of Dunham and associates (33) suggest that the Negro infants, both male and female, are more mature than white infants of the same sex and birth weight. In this connection Peckham (70) says: "It seems probable that the latter weight range [2,500-2,599 gm.] in the white race is about the equivalent in maturity of the 2,300 to 2,400 range level in the black." Brown, Lyon, and Anderson (18) also suggest that because of a racial difference in average birth weight the upper limit of birth weight for prematurity among Negro infants should be 2,350 gm. instead of 2,500 gm. (See p. 12.)

PLURALITY OF BIRTH

Peckham (70) found, in his series of 4,055 infants weighing less than 2,500 gm. at birth but measuring at least 35 cm., that with the exception of extremely immature infants of birth weights less than 1,000 gm. (2 lb. 3 oz.) the chances of survival were much greater for twins than for single-born infants in each 500-gm. weight group studied. Peckham regards this (p. 488) as "confirmation of the closer approach to maturity, at any given weight, of twin infants as contrasted with single-born children" Dunham and McAlenney (34, p. 717) say on this point: "Although infants of multiple birth are usually considered in the same category with single-born infants with regard to prematurity provided the birth weight is 2,500 gm. or less, many of them are born close to term or even at term and have had a longer period of gestation than single-born infants of the same weight, are therefore more mature and so are better prepared for extrauterine life."

Duffield and associates (32) report, however, that they did not find "any uniform or consistent differences between the mortality rates of single-born white infants and plural-born white infants of the same weight at birth. The higher neonatal mortality rate of the total group of plural-born white males (133 per 1,000 live births) compared with that of single-born white males (24) can be accounted for by the very much greater percentage of small infants among the plural-born white males. Likewise, the higher mortality rate of the total group of plural-born white females (125 per 1,000 live births) compared with that of single-born white females (18) can be accounted for by the very much greater percentage of small infants among the plural-born white females."

MATERNAL FACTORS

In a study of all the premature infants (244) born in the New Haven Hospital during the 10-year period 1924–33 Dunham and McAlenney (34) pointed out the importance of birth weight as a factor in mortality in relation to such conditions as parity of mother, complications of pregnancy, induced labor, abnormal duration of labor, and operative delivery. Later Breese (17) in a study of 987 premature infants, of whom 284 died, made a statistical analysis of conditions in the mother and factors at delivery influencing mortality of these infants in which he held the birth-weight factor constant. He found (p. 662) that "the age of the mother has very slight effect on premature infant mortality except in women over 40 years of age, whose infants have a slightly higher mortality rate than we would expect on a basis of weight." Among the complications of pregnancy and delivery that he studied only one (hydramnios) showed a significant relation to the mortality rate.

A number of studies have been made of the influence of birth weight on deaths of infants associated with various types of operative delivery. Cesarean section and other types of delivery have frequently been stated to result in higher mortality rates among premature infants. Peckham (70, p. 493) showed that among 3,077 deliveries of live-born premature infants weighing less than 2,500 gm. (5 lb. 8 oz.) or measuring less than 45 cm. (18 in.) in crown-heel length but meeting a minimum standard of either 1,500 gm. (3 lb. 5 oz.) in weight or 35 cm. (14 in.) in length the mortality varied widely with the type of delivery and also with the birth weight. (Table 20 is adapted from table 7, page 493, of Peckham's report.)

Peckham comments (p. 495), "It is not our belief that this table shows in any way the comparative risk rate to the infant according to the method of delivery, per se. In the vast majority of those cases delivered by operative means, breech extraction alone excluded, the choice was dictated by some maternal complication such as heart disease or placenta previa rather than through conscientious effort to produce a living infant. Consequently, the rates . . . would seem to reflect the mortality from the maternal abnormality rather than that associated with any given type of delivery." He says in conclusion (p. 497) that his analysis of mortality rates according to type of delivery "permitted no definite statement as to the most favorable procedure for the immature infant."

 TABLE 20
 Neonatal deaths per 100 live-born premature infants, according to birth weight and type of delivery (Peckham)

Type of delivery	Total, less than 2,500 gm.	1,499 gm. and less	1,500–1,999 gm.	2,000–2,499 gm.	
Spontaneous	18.06	68.78	30. 84	7. 69	
Operative	21.74	59.02	42. 22	7. 58	
Cesarean	25. 96	84. 62	31. 82	13. 04	
Breech extraction.	20. 40	35. 00	45. 31	4. 27	
Forceps.	9. 70	45. 45	21. 43	4. 59	
Version and extraction	34. 02	81. 25	53. 57	9. 43	

Miller (62) called attention to the primary importance of birth weight and the minor part played by type of delivery in relation to mortality when, in 1940, he presented data with regard to the effect of cesarean section on fetal and neonatal mortality and reviewed the studies on the subject. He analyzed records of 3,210 live births and stillbirths occurring over a period of years at the New Haven Hospital, 415 of which occurred after cesarean section. (Stillbirths were included unless death was known to have occurred before onset of labor or operation.) The number of live-born infants weighing 2,500 gm. or less at birth was 215, of whom 44 were delivered by cesarean section. Miller concluded that the total mortality among infants born after cesarean section is higher than that of infants born spontaneously or by low-forceps deliveries by virtue of the fact that "the incidence of premature-infant births is significantly higher in the former than in the two latter groups." This higher incidence of premature births is due in turn "to the significantly higher incidence of mothers with certain complications of pregnancy delivered by this method." Though the author comments that the number of premature infants in his study is too small to determine statistically the effect of the method of delivery on the mortality, "nevertheless the high mortality among premature infants born by cesarean section is largely referable to the fact that a very high proportion of infants weighing less than 1,500 gm. at birth were born by this method."

Of the 44 infants delivered by cesarean section, 20.4 percent (9 infants) weighed less than 1,500 gm., compared with 10.9 percent of those delivered spontaneously (13 of 119 infants) and 3.5 percent of those delivered by forceps (1 of 28 infants). Miller believes that "the mortality among live-born premature infants is determined almost wholly by their birth weight. It is not apparent that the type of delivery or the presence of complications of pregnancy in the mothers determines the viability of the live-born premature infant significantly."

There is considerable evidence that the earlier in pregnancy labor occurs the more likely is the infant to be delivered by the breech, and the less mature the infant who is delivered by this method the more dangerous the method. Miller analyzed his series of 3,210 births, of which 215 (6.7 percent) were live-born premature infants, to show the incidence of premature birth by method of delivery. Though the total number of breech extractions was relatively small (76) the incidence of premature birth among the infants so delivered (18.4 percent) was higher than its incidence by any other method of delivery.

The relation of breech delivery to mortality among premature infants is brought out by Beck (11), who calls this method extremely dangerous when the infant weighs less than 2,000 gm. because "in the young prematures the circumference of the shoulders and body is less than the circumference of the fetal head. When the cervix is dilated sufficiently to permit the passage of the shoulders, therefore, it is not large enough for the head. The aftercoming head, accordingly, is caught by the cervix, and the child either dies from asphyxia or from the injuries which are caused by the difficulties encountered in delivering the arrested aftercoming head."

In Beck's series of 473 infant deaths, 57 followed breech delivery. Of the infants weighing 1,000 to 1,500 gm. who were delivered by this method 70 percent died; of those weighing 1,500 to 2,000 gm., 50 percent died; and of those weighing 2,000 to 2,500 gm., 6.4 percent died, **a** proportion not markedly higher than the percentage of infants in this weight group who died from all causes (5.4).

Beck concluded that "spontaneous vertex delivery accompanied by episiotomy under local anesthesia is the safest method of delivery for premature infants."

According to Dieckmann (30), the incidence of breech presentation among fetuses 28 to 36 weeks in gestational age is 20 to 40 percent, compared with 4 to 5 percent at term. The average gross mortality for full-term infants delivered by the breech on five maternity services is given by Dieckmann as 7.7 percent, compared with 25 percent among the premature infants in his series delivered by this method. The deaths following breech delivery were attributed to prematurity (without other cause stated), intracranial injury, asphyxia, and, in a few cases, visceral injuries.

Clinical and postmortem studies

Determining the exact cause of death of a premature infant is often difficult. Postmortem examination will often throw light on the cause of death; but, even if clinical and postmortem examinations are made carefully, there will still be a large proportion of cases in which no

specific cause of death is determined, because many very immature infants, born alive, die simply because development has not advanced to the point at which extrauterine existence is possible. Failure to make a specific antemortem clinical diagnosis, however, may result from lack of clinical skill, inadequate laboratory techniques, or incorrect interpretation of clinical or laboratory findings, especially if knowledge of developmental changes is inadequate.

Dunham and McAlenney (34) reported for 66 premature infants the primary causes of death determined clinically in the infants and checked in more than half the cases by postmortem examinations, as shown in table 21.

TABLE 21	Principal cause of death of 66 prematurely born infants; clinical an	d
	postmortem diagnoses (Dunham and McAlenney)	

Cause of death	Clinical diagnosis	Postmortem diagnosis	Clinical diagnosis confirmed
Total	66	38	36
Prematurity alone . Infection (blood culture positive) . Intracranial hemorrhage Congenital defect. Other	34 16 11 3 2	14 11 11 0 2	14 9 11 2

In this relatively small series, prematurity without other cause played the chief role in causing death; infection (pneumonia, septicemia, respiratory infection, diarrhea, and meningitis) was second in importance; and intracranial hemorrhage (the result of birth injury) and congenital defect took third and fourth place, respectively. In 36 of the 38 cases in which postmortem examination was made the antemortem diagnoses were confirmed. In all the cases in which infection was the reported cause of death, antemortem or postmortem blood cultures were positive. In 2 of the cases no focus of infection was found postmortem.

In postmortem studies of 503 premature and "previable" infants Potter reported causes of neonatal death as shown in table 22. (Personal communication from Edith L. Potter, M. D., Chicago Lying-In Hospital. For other data with regard to these autopsies see 77.)

 TABLE 22
 Neonatal deaths of previable and premature infants¹ and causes of death as determined by postmortem examination (Potter)

	То	tal		Premature
Cause of death	Number	Percent	Previable	
Total	503	100. 0	155	348
No abnormalities Anoxia (asphyxia) Nonsyphilitic infections Hemorrhage, traumatic Malformations Miscellaneous Syphilis Blood dyscrasia	232 67 66 65 49 18 3 3	46. 1 13. 3 13. 1 12. 9 9. 7 3. 6 0. 6 0. 6	111 9 17 15 3 0 0 0	121 58 49 50 46 18 3 3

¹ The infant is placed in the previable or the premature group if at least two of the following criteria are present: Previable—length, 28.0-34.9 cm.; weight, 400-999 gm.; gestation, 22 through 28 weeks; premature—length, 35.0-46.9 cm.; weight, 1,000-2,499 gm.; gestation, 29 through 38 weeks. (76, p. 31.)

Prematurity alone (no abnormalities) was found to be the chief cause of death (46 percent). Among the 232 cases found on postmortem examination by Potter to have **no abnormalities** nearly half (111) were in the group of very small infants classified by her as "previable." (For definition see table 22, footnote.) These 111 "previable" infants with no abnormalities made up 72 percent of the entire "previable" group (155). Anoxia, nonsyphilitic infections (mostly pneumonia), and hemorrhage were next in frequency, each accounting for 13 percent of the deaths. Malformations accounted for 10 percent.

Potter and Adair (76, pp. 107, 109) distinguish between primary and secondary anoxia, the former being the type classified by them as a primary cause of death, the latter as a contributory cause. Death from primary anoxia (asphyxia) occurs when oxygenation of the fetal blood is interfered with by certain maternal diseases, by certain types of sedatives and anesthetics given to the mother during labor, or by placental and cord conditions. Primary anoxia is therefore always intrauterine in origin although the infant may not succumb until after birth. In the cases in which death is ascribed to primary anoxia the characteristic postmortem findings, according to Potter and Adair (77, p. 1055), are "discrete petechial hemorrhages in the lungs or thymus and/or petechial hemorrhages in the brain substance. The latter were often visible only on microscopic examination."

The postmortem findings in deaths due to nonsyphilitic infections, birth trauma, and malformations are included in the sections on these conditions.

Certain conditions are often certified by physicians as causes of death which are not acceptable according to the rules of the National Office of Vital Statistics. (See appendix 1, p. 363.) Chief among these are atelectasis and thymic hyperplasia.

In the reports cited, *atelectasis* does not appear among the primary causes of death. This is in accord with the belief, now generally accepted, that atelectasis is always secondary to some other condition, though it continues to be recorded not infrequently on death certificates as the cause of infant death. Potter (74, p. 137) states in this connection:

"The lungs of a stillborn fetus are always completely nonaerated providing attempts at resuscitation have not been carried out. Even in the normal live-born infant expansion is a gradual process, and the lungs of practically all infants who die within the first few days of life contain much less air than do those of older individuals. Terminal resorption of air also frequently occurs, so that at autopsy some degree of nonexpansion, so-called atelectasis, is almost invariably found.

"Atelectasis is not to be considered a cause of death. Although nonaeration of the lungs may be the immediate reason for failure to survive, the atelectasis is only a symptom of some underlying abnormality. The pathologist may intend the term atelectasis to be purely descriptive, but it is too often directly transferred to the death certificate."

Thymic hyperplasia was formerly considered to be a frequent cause of infant death. The diagnosis was based on roentgenographic demonstration of a wide mediastinal shadow interpreted as the thymus, or the finding at postmortem examination of what was interpreted as an "enlarged thymus." This diagnosis is now rarely made. Boyd

(15, p. 879) has shown that "in general, the fluctuations in the weight of the thymus at any age period are concomitant with fluctuations in body weight," and that the fetal type of thymus is broad, whereas the infantile type is elongate. This change in form is produced during the first 2 weeks of life as the result, according to Noback, of gradual expansion of the lungs. The shadow of the gland as seen in roentgenograms is known to vary greatly with the phase of respiration at which the exposure is made, and symptoms ascribed to "enlarged thymus" are not pathognomonic. Potter and Adair (76, p. 165), in approximately 2,000 autopsies on infants under 1 year of age, did not find a single case that would justify a diagnosis of "status thymicolymphaticus." They also cited an exhibit of the New York City medical examiner showing that a majority of the deaths reported as due to "status thymicolymphaticus" had been found at autopsy to be due to "an acute infection, mechanical obstruction of air passages, or other anatomic lesions."

Postmortem diagnoses of causes of death of premature infants, although more exact than clinical diagnoses, have their limitations also, since even the most skilled pathologists, in a large proportion of the cases examined, can determine no specific cause of death. In addition, it is difficult to interpret postmortem pathology, especially that of the central nervous system.

Postmortem examination of all premature infants offers advantages to the physician, whether or not he has determined the cause of death clinically. The difficulty of clinical diagnosis of morbid conditions in these infants is recognized, and surprises at the autopsy table frequently confront the most skilled clinician. When the cause of death is undetermined or questionable or the morbid condition is found to have been incorrectly diagnosed the information obtained at postmortem examination will often lead to improvement in diagnostic procedures and re-evaluation of methods of treatment.

The benefit to be expected from this type of examination is, of course, dependent on the expertness of the pathologist and the correlation of the findings with the medical history and physical examination of the infant. The responsible medical staff should be present when the examination is made. In addition, cases of special interest should be the subject of clinical-pathologic conferences attended by members of the professional staff of the hospital.

Summary

NATIONAL STATISTICS

"Premature birth" is the chief cause of death in the period of infancy. In continental United States it accounts for nearly one-third of the deaths of the first year and nearly one-half of those in the first month of life. But deaths attributed to premature birth do not represent the total loss of life associated with prematurity, because deaths of infants attributed to other causes, especially other prenatal and natal causes, include those of some infants that are premature.

The neonatal mortality rate for premature birth for the United States decreased 23 percent in the 10 years 1935-44. The rate for Negro infants is higher than that for white infants and decreased less rapidly. Almost all the deaths from premature birth take place in the first month (97 percent in 1944). More than half of those in the first month take place on the first day (57 percent in 1944).

There are wide variations among the States in the neonatal mortality rate for premature birth. Among the States that in 1940 had at least 90 percent of their births registered the rate varied in 1944 between 8.9 and 17.6 per 1,000 live births. In continental United States the rate was 11.5 in 1944.

In the 11 States and the District of Columbia which had the most nearly complete birth registration (at least 98 percent in 1940) the neonatal mortality rate for premature birth for the triennium 1942–44 ranged from 9.3 for Connecticut to 16.2 for the District of Columbia. These States and the District of Columbia all showed decreases in the rate in 1942–44, compared with 1933–35, that ranged from 23.4 to 32.6 percent.

HOSPITAL STATISTICS

Hospital statistics on deaths of premature infants are reported as fatality rates (deaths per 100 premature infants born in or admitted to the hospital). Figures from different hospitals are difficult to compare because they have not been compiled uniformly. A few hospitals have reported data collected and analyzed in conformity with the recommendations of the American Academy of Pediatrics; namely, to include all live-born infants weighing 2,500 gm. or less and to analyze the fatality rates in four birth-weight groups.

For different periods between 1922 and 1940 fatality rates ranging from 18 percent to 32 percent among all infants that weighed 2,500 gm. or less were reported from 12 hospitals. The fatality rates in each birth-weight group varied widely in these hospitals, but in general they were inversely proportional to the birth weight.

Reports from 6 hospitals for different periods between 1940 and 1945 with regard to fatality rates similarly compiled show lower rates in all birth-weight groups. The fatality rate for all infants weighing 2,500 gm. or less ranged from 15.0 to 27.4 percent. The 4 hospitals that reported fatality rates for both periods had considerably lower rates for the later period. The rates within each birth-weight group varied less widely among these 6 hospitals than among the 12 hospitals reporting earlier.

For more detailed and statistically valid comparisons of fatality rates of different hospitals and at different periods further studies are needed, based on uniform methods of compiling the necessary information. For this purpose the recommendations of the American Academy of Pediatrics should be strictly adhered to. A suggested summary form for compiling information on hospital births and deaths of premature infants, by weight and race, is presented for consideration (appendix 8, p. 389). Comparative studies of fatality and survival rates among premature infants will assist hospitals to evaluate their methods of care.

FACTORS INFLUENCING MORTALITY

Factors that have been reported as influencing mortality of premature infants are birth weight, race, sex, plurality of births, the mother's age and parity, and complications of pregnancy and delivery.

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When a birth weight of 2,500 gm. or less is used as the criterion of prematurity, the mortality rate is inversely proportional to the birth weight. The mortality rate is higher among Negro premature infants than among white, and is higher among males of both races than among females. The racial difference has been shown to be closely related to difference in birth weight. Plural-born infants have a higher mortality rate than single-born infants. This difference also has been found to be related to birth weight.

The mother's age, unless she is over 40, is reported to have little influence on mortality rates of premature infants. Complications of pregnancy, also, have not been shown to influence premature-infant mortality except insofar as they result in the birth of infants of low weight.

Certain types of operative delivery have been shown to be associated with high premature-infant mortality. The high proportion of infants of low birth weight among those born to mothers who are delivered by operation appears to influence the mortality rather than the type of delivery per se. Breech delivery, however, is associated with higher premature-infant mortality, especially among the lower weight groups, than would be accounted for by the low weight alone. Breech presentations are much more common among premature than among mature infants.

CLINICAL AND POSTMORTEM STUDIES

Determination of the exact cause of death of premature infants is often difficult. The causes of death reported will vary with the completeness of antemortem clinical and laboratory diagnosis and with the expertness of the pathologic examination. For example, in a series of cases from a hospital in which antemortem and postmostem blood cultures were almost routine, infection was found to be the second most frequent cause of death. In a much larger series in another hospital, anoxia was listed as the second cause and nonsyphilitic infections as third. However, in one of these series the chief cause of death was "prematurity"; in the other it was "no abnormalities." In the latter series nearly one-third of the infants were classified as "previable," and more than 70 percent of the deaths of these less mature infants were included under the term "no abnormalities."

Atelectasis and thymic hyperplasia (status thymicolymphaticus) were formerly reported as primary causes of death, but this is no longer considered acceptable. Atelectasis is always secondary to some other cause. Symptoms from so-called enlarged thymus are not pathognomonic, and careful postmortem examination in deaths reported due to this condition often reveals some unrelated pathologic condition that accounts for death.

Postmortem examinations of premature infants by skilled pathologists are of value, though even the most skilled pathologist will find it impossible, in a considerable proportion of the cases, to assign a specific cause of death. Results of postmortem examination, when correlated with the medical history and the physical examination of the infant, will often yield information that will lead to improvement in diagnostic procedures and re-evaluation of methods of treatment.

PHYSICAL GROWTH OF PREMATURE INFANTS

Knowledge of some aspects of growth of premature infants is of practical value to the clinician. Standard curves of growth in weight and length are useful for determining the maturity of an infant, as well as the gains to be expected in a given period, and the attempt will be made here to present figures that are most significant from a practical point of view. 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 physiologic development will therefore precede consideration of growth in weight and height.

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 so-called term birth. To bring out these variations in the antenatal growth of different organs Ballantyne (9, p. 10) has presented graphically (see fig. 5) a "corrected scheme of antenatal life," which he describes 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. In order to represent this fact graphically I have carried a projection of embryonic life up through the neofetal, fetal, and neonatal periods into the postnatal. 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 Again, the germinal period does not abruptly stop at the and trunk. 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. This is indicated in the scheme, which also represents in a graphic form the continuity of the germ plasm and of germinal life."

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Figure 5.—Scheme of antenatal life (from Ballantyne, J. W.: Manual of Antenatal Pathology and Hygiene—The Foetus. Edinburgh: Green, 1902).

Development of body form and individual organs

Arey (7, p. 105) describes fetal development as follows:

"During the *third month* (lunar) the fetus definitely resembles a human being, but the head is still disproportionately large [see fig. 6]; the umbilical herniation is reduced by the return of the intestine into the abdomen; the eyelids fuse, nails begin forming, and sex can now be

Physical Growth of Premature Infants



Figure 6.—Human embryos and fetuses, 12 weeks, 16 weeks, 5 months, and 6 months old; one-half actual size (adapted from Patten, B. M.: Human Embryology. Phila.: Blakiston, 1946).

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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."

Arey states that "after the second month the developing young is commonly called a *fetus.*" This metamorphosis is due principally, he says, to the following factors:

- 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 of the internal organs are well laid down at 2 months; henceforth, until the end of gestation, the chief changes undergone are those of growth and further tissue differentiation.

Changes in growth of organs and tissue differentiation are shown in the following list. Items have been selected from Arey's table which might be helpful in making clinical judgment of age and which have significance from the point of view of function. Since the end of the 7th month (28th week) is the period usually considered the earliest at which extrauterine existence is possible, data are given for developments found to have been attained at this period.

CORRELATED HUMAN DEVELOPMENT

(Material selected from A	Arey (7, facing p. 106). Figures in parenthesis refer to fetal age in lunar months.)
Integumentary system	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) Lanugo hair appears (5) Hairs emerge (6)
Mouth	Palate fusion complete (3) Enamel and dentine depositing (5) Lingual tonsil forming (5) Permanent tooth primoria 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 mucosa of gut pres- ent (5) Ascending colon becomes recognizable (6) Deep esophageal glands indicated (7)
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 $(1\frac{1}{2})$ Main blood vessels assume final plan (2) Enucleated red cells predominate in blood $(2\frac{1}{2})$ Blood formation in bone marrow beginning (3) Heart musculature much condensed (4) Blood formation increasing in bone marrow and de- creasing in liver $(5-10)$ Spleen acquires typical structure (7)
Nervous system	Commissures [of brain] completed (5) Myelinization 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)

Growth in weight and length

VALIDITY OF WEIGHT AND LENGTH STUDIES

Adequate figures for growth in weight and length are available for full-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 prenatal-growth curves. Such material on prenatal growth is voluminous, but it provides a shaky foundation for a standard growth curve because of disagreements in figures and in their interpretation, the small numbers on which some of the studies are based, and fundamental differences in method.

Studies on prenatal growth are based largely on measurements of dead fetuses or sometimes, for the later months that are of primary importance, on measurements of both dead fetuses and living premature infants. In the earlier studies especially, allowances were not always made for the effects of preservatives on the weight and length of the fetuses. Measurements of fetuses are difficult and techniques of measurement varied in different studies and with different observers. Some authors who have been widely quoted have made composite averages of the figures of other investigators, and though this procedure gives the advantage of larger numbers, their results, based on different combinations of previous studies, are discouragingly far apart.

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. The only procedure that is statistically satisfactory for establishing growth standards is repeated measurements of the same individuals at stated intervals. This is obviously impossible in the prenatal period, and such 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, almost all the figures are averages and 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 need for new growth studies of premature infants is apparent from this discussion. Such studies are particularly needed because of the better understanding in recent years of the nutritional and other requirements peculiar to premature infants, which are being met to a limited, but slowly increasing, extent as the newer knowledge is disseminated.

PRENATAL GROWTH

From a practical standpoint it seems unnecessary to repeat here figures on prenatal growth in weight and length from the earlier studies, most of which were German, but reference will be made to those frequently quoted. In recent years newer techniques and standards of fetal anthropometry have been developed, and some data on less restricted racial groups are available.

European studies

Among the earlier German studies that are frequently quoted are those of Daffner in 1902 (28), Friedenthal in 1914 (38), and Zangemeister in 1911 (109). Friedenthal combined measurements from various studies in presenting monthly averages for prenatal weight and length. Zangemeister 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 prenatal life, together with the average weight and length of 11,181 full-term infants (tenth month); his averages are based on combined figures of earlier investigators. Daffner gave upper and lower limits of weight and length for each month instead of single averages; his figures are therefore not comparable with the others except as Zangemeister shows graphic zones of growth; but the wide limits of Daffner's groups give an interesting indication of the extent of individual variation.

Ylppö (107), who in 1919 presented average figures based on the research of previous investigators, comments:

"... we have so far no reliable growth curves for intrauterine life.... As could be expected, the answers to the question how much a human fetus must weigh at a given age differ even more than the figures for the average length; for the first 5 months the figures are particularly unreliable. Fortunately this circumstance is not very important for us because we wish to obtain reliable average figures for viable premature infants, and these are not present among fetuses less than 5 months old. For the subsequent months of pregnancy the material is much more abundant and the figures are more reliable; but here too great differences have been observed among the averages given by the different writers. Zangemeister's data are the most reliable, being based on particularly careful and extensive observations. It is interesting to note that the total averages of all the writers [as computed by Ylppö] are strikingly near Zangemeister's figures. The figures given by Friedenthal for the weight of fetuses in the different months are no doubt much too high and I emphasize this fact because his figures are often used as a basis for various reports on growth. . . ."

Ylppö studied the growth of 700 premature infants (birth weight 2,500 gm. or less), some of whom he observed over a period of years. He based his conclusions with regard to extrauterine growth on comparisons with intrauterine-growth curves, which he derived from a number of the earlier investigators in addition to those combined by Zangemeister. Ylppö's combined averages for weight and for length are shown in table 23 and in figure 7. To facilitate comparisons monthly increments have been computed.

With regard to these combined averages Ylppö comments (p. 119): "Of course we must realize that the deviations from these normal curves may be quite considerable in the individual case, even though the growth in that case is not pathologic." Seven fetuses for which he had the exact conceptional ages (table 24) varied so much that he made them the occasion for a warning as to the wrong conclusions that may be drawn from data based on too few cases.

North American studies

Of the American investigators Scammon and Calkins have done the most comprehensive research on body measurements, using their own

Lunar month	Average weight (gm.)	Increase ¹		Average	Increase ¹		
		Gm.	Percent	length (cm.)	Cm.	Percent	
12 33 45 67 87 91001000_10000_1000000	1.0 3.4 29.88 92.4 254.8 633.2 1,150.0 1,644.6 2,281.3 3,065.8	2. 4 26. 48 62. 52 162. 4 378. 4 516. 8 494. 6 636. 7 784. 5	240 779 209 176 149 82 43 39 34	0.7 2.8 8.0 13.7 21.5 30.1 35.6 40.2 45.0 50.0	2.1 5.2 5.7 7.8 8.6 5.5 4.6 4.8 5.0	300 186 71 57 40 18 13 21 11	

TABLE 23 Average weight and length in each lunar month of prenatal life (computed by Ylppö from earlier studies)

¹ Computed from Ylppö's figures.

material and that of previous investigators in statistical calculations with regard to the interrelationships of certain body dimensions. Curves of five observers (Mall, 1910; Zangemeister, 1911; Heuser, 1912; Lacassagne, 1909; and Streeter, 1920) showing body length and fetal age were cited by Scammon and Calkins as being "remarkably consistent." The median, that of Mall, they selected as the basis for their empirical length-age formula. (See p. 63.)




TABLE 24	Weight and	length o	f seven	fetuses	whose	exact	conceptional	age	was
	known (Ylpr	ю) [–]					-	-	

Duration of pregnancy			
Days	Lunar months	Weight (gm.)	Length (cm.)
145	5. 18 5. 46 5. 71 7. 14 7. 32 8. 04 10. 00	1, 670 1, 050 1, 118 980 400 1, 200 1, 900	38. 4 37. 0 34. 5 31. 0 39. 5 44. 0 46. 5

Mall's figures for length of the embryo and fetus are based on approximately 2,000 cases, about half from his own collection and the remainder from published sources and from correspondence (57). He presents a formula for estimating age from crown-rump length. Table 25 shows Mall's figures for both crown-rump and crown-heel length for each lunar month of prenatal life, his final figures being for $38\frac{4}{7}$ weeks, or 270 days, the mean duration of the period from conception to term, rather than 280 days, the period from the first day of the mother's last menstrual period to term. The columns showing monthly increases have been added to facilitate comparison with other figures cited. Except for the early months, which show great variations in all the studies, and the final line, which is for a different period, the figures for crown-rump length are generally similar to Streeter's, which are shown in table 26.

For the length of the fetus some investigators prefer crown-rump and others, crown-heel measurements, and formulas have been devised to convert figures from one to the other. Though Mall (56) gives figures for both and refers to crown-rump measurements as "standard," he says that in measurements of 600 embryos he did not find one measurement more variable than the other and that the crown-heel measurement has the advantage of being the one "usually made by obstetricians as well as anthropologists." Scammon and Calkins (85) concluded, after experimental and statistical studies of actual measurements of "preserved, fresh-dead, and living material," that the

	Mean c	rown-rump	length	Mean crown-heel length			
Probable age in lunar months		Increase ¹		G -1	Increase 1		
	Cm.	Cm.	Percent	Cm.	Cm.	Percent	
1	0.25 2.5 6.8 12.1 16.7 21.0 24.5 28.4 31.6 33.6	2.25 4.3 5.3 4.6 4.3 3.5 3.9 3.2 2.0	900 172 78 38 26 17 16 11 6	$\begin{array}{c} 0.\ 25\\ 3.\ 0\\ 9.\ 8\\ 18.\ 0\\ 25.\ 0\\ 31.\ 5\\ 37.\ 1\\ 42.\ 5\\ 47.\ 0\\ 50.\ 0\end{array}$	2.75 6.8 8.2 7.0 6.5 5.6 5.4 4.5 3.0	1, 100 227 84 39 26 18 15 11 6	

TABLE 25 Crown-rump and crown-heel length in each month of prenatal life (Mall)

1 Computed from Mall's figures.

Age in luner months	Formalin weight	Incre	ase 1	Crown- rump	Increase ¹			
Age in tunar montus	(gm.)	Cm.	Percent	length (cm.) ¹	Cm.	Percent		
2 3 5 6 7 8 9 10	$\begin{array}{c} 1.1\\ 14.2\\ 108.0\\ 316.0\\ 630.0\\ 1,045.0\\ 1,680.0\\ 2,478.0\\ 3,405.0 \end{array}$	13. 1 93. 8 208. 0 314. 0 415. 0 635. 0 798. 0 927. 0	1, 191 661 193 99 66 61 48 37	2.3 6.1 11.6 16.4 20.8 24.7 28.3 32.1 36.2	3.8 5.5 4.8 4.4 3.9 3.6 3.8 4.1	165 90 41 27 19 15 13 13		

TABLE 26 Formalin weight and crown-rump length in each month of prenatal life (Streeter)

¹ Streeter gave his figures for length in millimeters and showed variation from week to week instead of from month to month. The monthly increases have been calculated from his figures.

"error in determination of crown-heel length . . . seems somewhat less, relatively, than that of crown-rump length." According to Meredith this has been confirmed in an unpublished study by Goodman in which two trained anthropometrists made independent measurements of crown-heel and crown-rump lengths of 100 normal newborn infants. The median of the differences in the two sets of measurements was 1.6 mm. for crown-heel length and 2.1 mm. for crown-rump length. (Goodman, J. L., Physical Growth of Infants From Birth to Three Months. Master of Arts Thesis, University of Iowa, 1941. Personal communication from H. V. Meredith, Ph. D., Iowa Child Welfare Research Station, State University of Iowa, Iowa City, Oct. 7, 1947.)

Streeter (96) presented data on prenatal 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 prenatal life. He did not show his material by sex 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 percent greater than fresh weight, and for this reason 5 percent was added to the figures taken from Zangemeister (109). These figures were then converted to mean crown-rump length by means of a correlation curve.

Streeter's figures for both weight and length show a steadily decreasing *percentage* of gain during the prenatal period. The *amount* of gain in length, however, shows strikingly little variation, while the *amount* of gain in weight increases as strikingly from month to month.

Scammon and Calkins (83) reported growth data based on measurements of 2,202 dead embryos and fetuses, as well as 5,674 observations of a small number of "living fetuses and newborn children." (For data on living infants see p. 66.) They found that the weights of live-born and dead-born 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 differences in the relation of body weight to body length were noted in either the living or the dead material."

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On the basis of their own measurements and the figures of Mall they present formulas by which the lineal growth of the human fetus for certain age periods can be calculated (82), the relation between body length and body weight can be shown (83), and the relation between body weight and age can be shown (84). Figure 8 shows in graphic form the relation between body weight and body length and fetal age, according to Scammon and Calkins' empirical formulas. Scammon



Figure 8.—Body weight and body length in prenatal life (calculated from Scammon and Calkins' formula).

and Calkins' figures (84) for calculated fetal dead weight and fetal length according to fetal age are shown in table 27. The authors considered their formulas accurate from the fetal age of $2\frac{1}{2}$ months.

POSTNATAL GROWTH

Much of the information on postnatal growth of the premature infant found in the 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. Obviously important factors influencing size (length and weight) of infants, which have not all been considered in any one study reported, are:

Premature Infants

- 1. The parents—race, height and weight, economic status, and mother's age, parity, general health and nutrition (especially during the prenatal 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.

TABLE 27	Dead weight and crown-heel length in each month of prenatal lif	e
	(Scammon and Calkins' empirical formulas)	

	Weight	Incre	ease 1	Crown-	Incre	ease 1
	(gm.)	Gm.	Percent	(cm.)	Cm.	Percent
2.5	3. 63 12. 00 73. 256. 561. 988. 1, 537. 2, 208. 3, 001.	8.37 61. 183. 305. 427. 549. 671. 793.	231 508 251 119 76 56 44 36	$\begin{array}{c} 3.53\\7.99\\15.89\\22.91\\29.24\\35.12\\40.58\\45.70\\50.53\end{array}$	4. 46 7. 90 7. 02 6. 33 5. 88 5. 46 5. 12 4. 83	126 99 44 28 20 16 13 11

¹ Calculated from Scammon and Calkins' figures.

A fundamental question, from the point of view of clinical use of the available material comparing prenatal with postnatal growth, is whether the newborn healthy premature infant tends to gain at approximately the same rate as the fetus of the corresponding conceptional age. Though investigators are not in full agreement the weight of opinion seems to point to such a growth tendency, though some retardation is indicated for varying periods.

European studies

Reiche (78, p. 382) concluded that the act of birth does not interfere with growth and that there is no difference in the rate of growth of premature infants and fetuses of the same conceptional age provided the premature infants were healthy, had not suffered injury at birth, and had attained sufficient maturity to survive in an extrauterine environment. This would mean that a premature infant, irrespective of his age at birth, would gain at the same rate from the tenth to the eleventh month of conceptional age as a full-term infant in his first month after birth. This conclusion was based on a study of 73 healthy premature infants born at the Kaiserin Auguste-Victoria Hospital in Berlin, or admitted after birth, and weighed and measured at the hospital at intervals through the conceptional age of 11 months. The number of infants in each of four birth-weight groups, with the corresponding lengths, was as follows:

	Number of infants
Total	- 73
800–1,200 gm., 32–40 cm	7
1,200–1,500 gm., 37–44 cm	16
2,000–2,000 gm., 40–48.5 cm 2,000–2,500 gm., 41.5–50 cm	29 21

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Table 28 shows the average weight and crown-heel length of the 73 premature infants studied by Reiche from the seventh to the eleventh month of conceptional age, together with monthly increases in weight and length computed from Reiche's figures. Reiche computed his averages from the weight and length of all infants of the conceptional ages specified, whether those ages were reached at birth or later in the hospital.

 TABLE 28
 Average weight and crown-heel length of 73 premature infants at specified conceptional ages (Reiche)

	A verage	Incre	ease 1	A verage crown-	Increase 1		
Age in lunar months	weight (gm.)	Gm.	Percent	heel length (cm.)	Cm.	Percent	
7	1, 190 1, 820 2, 340 2, 810 3, 330	630 520 470 520	53 29 20 19	37.5 41.75 46.0 48.9 51.5	4, 25 4, 25 2, 9 2, 6	11 10 6 5	

¹ Reiche computed the actual growth and the rate of growth on a yearly basis; i. e., the growth for a year at the figure for each month. The increases given in the table have been calculated on a monthly basis from Reiche's monthly average figures for weight and length.

Sex differences were not reported by Reiche, who said that for the tenth and eleventh months the number of infants was not sufficient for study of this factor. Another point that should be noted is that he measured the infants in the "hanging" position. His figures for length are therefore not wholly comparable with results found in studies to be discussed later in which the crown-heel measurements were taken in the prone position.

Reiche comments that his figures are somewhat below "normal" figures; he attributes this to the fact that his averages, particularly those for the eleventh month, were based on the weaker infants, who had remained longer in the hospital. In spite of this, he says, there was in the eleventh month a rise in the weight increase and in the percentage of weight increase, which "completely agrees with the rule of growth for the first month after birth." He comments also on the increase in length as being the same in the eleventh and in the tenth month.

Reiche's figures, however, when the percentage change is calculated by comparison of the later month with the preceding month, actually show slight declines in the percentage increases in both weight and length from the tenth to the eleventh month, though the absolute increase in weight rose, as table 28 shows.

Reiche's "rule" that the percentage of increase is greater in the eleventh month of conceptional age, which he derived from Friedenthal, is not supported by the figures of other investigators, who show decline in *rate* of growth beginning in prenatal life and continuing without a break after birth. However, Scammon and Calkins agree with Reiche's general conclusion that premature infants tend to grow at the fetal rate except that, according to these authors, growth in the first month after birth is retarded by the necessity of adjusting to extrauterine conditions.

The 700 premature infants studied by Ylppö (107, p. 127) were grouped by weight as follows:

Premature Infants

		Number of infants
Tota	1	700
600-1,000	gm	
1,000-1,500 1.501-2.000	gm gm	208 253
2,001-2,500	gm	202

Nearly half of these infants died before the end of their first year; for the others growth was followed at intervals, in one case until the end of the ninth year.

Ylppö compares the growth of the premature infant with an intrauterine-growth curve and with figures for growth of the fullterm infant. "The normal growth impulse in premature infants is enormous . . . and the younger the child [in conceptional age] the more intense is the growth. We must not, however, on this account deceive ourselves when, for instance, the weight curve of a premature infant rises; this by no means signifies that the weight is increasing sufficiently. In evaluating the increase in weight and the growth in general we must use different standards in each case, according to the individual's [conceptional] age. The so-called increased growth potential of premature infants . . . is nothing more than an expression of the impulse of premature infants to follow the laws of growth corresponding to their [conceptional] age."

Ylppö (p. 164) concluded, however, that in premature infants these laws of growth are temporarily interfered with by factors due to the prematurity. Almost all of Ylppö's group of premature infants showed disturbances of growth in both weight and length, which he considered to be "inevitable consequences of premature birth" and due largely to nutritional deficiency and rickets. (See p. 85.) Those weighing less than 1,000 gm., as would be expected, took longer to overcome their handicap. At 3 months after birth this group weighed 1,600 to 2,000 gm., compared with the 3,000 gm. that Ylppö takes as the average weight of an infant 9 months in conceptional age. These premature infants at 9 months after birth, or 15 months in conceptional age, measured only 55 cm. compared with an average of 66 cm. for fullterm infants of the same conceptional age. Though the smallest infants showed the most extreme retardation, all the premature infants studied except a few in the higher weight groups showed a retardation in growth that was not overcome for a considerable period. (For discussion of later development of Ylppö's group of premature infants see p. 83.)

According to Zeltner (110), the increased growth potential of the premature infant is hardly apparent in the lowest weight group (1,000-1,500 gm.), and in the other groups it loses its force after the postnatal months that would normally have been intrauterine. Tables 29 and 30 show monthly increase in weight and length in the first 9 months of life for the 700 premature infants studied by Zeltner in the Nürnberg Infant Home. Zeltner himself made all the observations.

Weight and height increments of North American infants

Scammon (81) reported the average monthly percentage increments in weight, in three birth-weight groups, of 78 living premature infants compared with the monthly percentage increments in weight of full-

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TABLE 29 Increase in weight of premature infants in the first 9 months of postnatal life, by birth-weight groups, and of full-term infants in the first 6 months (Zeltner)

		Increase (gm.) in—										
Birth-weight group	lst mo.	2d mo.	3d mo.	4th mo.	5th mo.	6th mo.	7th mo.	8th mo.	9th mo.			
1,000–1,500 gm 1,500–2,000 gm 2,000–2,500 gm Full-term infants	167 400 429 533	640 847 917 685	694 797 703 590	638 732 543 488	650 605 581 548	647 539 590 497	587 475 564	500 454 575	433 319 417			

TABLE 30 Increase in length of premature infants in the first 9 months of postnatal life, by birth-weight groups (Zeltner)

		Increase (cm.) in—										
Birth-weight group	1st mo.	2d mo.	3d mo.	4th mo.	5th mo.	6th mo.	7th mo.	8th mo.	9th mo.			
1,000–1,500 gm 1,500–2,000 gm 2,000-2,500 gm	1.5 2.4 3.2	3. 1 3. 4 3. 3	3. 3 3. 2 3. 7	3. 3 3. 4 2. 5	3.5 3.2 2.6	2.7 2.0	2.7 1.2	1.7 1.5	1.5 1.3			

term infants as averaged from 10 large series of published observations. (See table 31.) He based his figures on all premature infants who made any gain in weight in the first month after birth. He gives percentages only, not amounts of increase.

The author commented on table 31 as follows:

- 1. The percentage increment in weight of prematures in the first postnatal month is lower than in the second month and following the second month the rate of increment gradually decreases.
- 2. The percentage increments are, in a general way, inversely proportional to the birth weight.

TABLE 31	Average monthly percentage increments in body weight of prematu	re
	and full-term children in infancy (Scammon)	

	Birth-weight group						
Month of life	1,000-1,500 gm. (average 1,300 gm.) 17 cases	1,500-2000 gm. (average 1,720 gm.) 35 cases	2,000-2,500 gm. (average 2,300 gm.) 26 cases	C. 2,750-c. 4,200 gm. (average 3,380 gm.) ¹			
First month	Percent increase 22.8 45.1 24.5 21.1 16.2 14.4 11.6 7.4 5.1	Percent increase 16.8 31.6 20.4 17.2 13.6	Percent increase 13.8 26.7 15.5 13.5	Percent increase 21.2 19.4 14.6 11.4 8.9 5.8 5.9 3.9 4.0			

¹ Average of 10 large series of published observations.

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Premature Infants

Scammon (81) also compared monthly weight-increment rates of the 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."

Results of a long-term study by Mohr and Bartelme (64) of the weight and height at various ages of premature white boys and girls (those weighing less than 2,500 gm. at birth) are shown in table 32 for

		We	ight		Height				
Age (months) 1	Bo	Boys Girls		Girls		ys	Girls		
	Number	Mean (kg.)	Number	Mean (kg.)	Number	Mean (cm.)	Number	Mean (cm.)	
3 6 9 12 18	5 5 3 22	4, 05 6, 15 7, 95 8, 92 10, 56	3 6 9 13 29	4.58 6.75 8.25 9.13 10.17	5 5 3 22	53, 50 62, 50 68, 50 74, 17 80, 11	3 6 9 13 29	55. 83 63. 75 67. 78 72. 12 80. 00	

 TABLE 32
 Weight and height of prematurely born white boys and girls at various ages up to 18 months (Mohr and Bartelme)

¹ Chronological age corrected for prematurity.

the first 18 months. The ages given are chronological ages adjusted to allow for the amount of prematurity. The children, the authors state, belonged to "a slightly inferior socio-economic group," but, on the other hand, they received superior postnatal care. It will be noted that the number of infants studied in the first year of life was small. (Additional data and conclusions based on the entire period of study are given under Prognosis, p. 85.)

Effect of atmospheric conditions

Growth in length of premature infants, in contrast to the findings just cited for growth in weight, proceeds at a markedly slower rate than in the fetal period, according to Blackfan and Yaglou (14). They reported the monthly gain in length for the first 3 months of a group of premature infants of specified fetal ages at birth in the air-conditioned nurseries of the Infants Hospital in Boston, as shown in table 33.

The increase in length was markedly greater for infants of all fetal ages in the second month than in the first and somewhat greater in the third month than in the second. The youngest infants at birth (those under 7 months in fetal age) increased in length more rapidly than those 7 months of age or over at birth, and this difference was specially noticeable in the second and third months.

Meredith (60, p. 71) comments that the figures of Blackfan and Yaglou may be "appropriately compared with gains for (a) intrauterine fetuses of similar age and (b) extra-uterine infants born at

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Physical Growth of Premature Infants

term. Under normal uterine conditions, the increment in stature of the average fetus between about 6 and 8 months of age is upward of 5 cm. per month. For full-term white infants the average monthly gains approximate 3.9 cm. between birth and 1 month, 3.3 cm. between 1 and 2 months, and 2.8 cm. between 2 and 3 months." (These figures for fetal growth in length are in general agreement with those of Ylppö, p. 60; Mall, p. 61; and Scammon and Calkins, p. 64.)

Blackfan and Yaglou (14) also studied the average weekly gain in weight of infants under different atmospheric conditions. Table 34

TABLE 33Average monthly increase in length of premature infants in air-
conditioned nurseries, according to fetal age; 1926-29 (Blackfan and
Yaglou)

	F	'irst mon	th	Second month			Third month		
Fetal age in months	Num-	A verage increase		Num-	A verage increase		Num-	A verage increase	
	ber	In.	In. Cm.	ber	In.	Cm.	ber	In.	Cm.
Total	96	0. 65	1.7	62	0.99	2.5	26	1.14	2.9
Under 7 7 to 8 8 or over Unknown	12 47 33 4	. 66 . 65 . 64 . 63	1.7 1.7 1.6 1.6	10 30 18 4	1.09 .96 1.00 .88	2.8 2.4 2.5 2.2	7 15 4	1.22 1.13 1.02	3.1 2.9 2.6

TABLE 34Average weekly gains in weight under various air conditions (Blackfan
and Yaglou)

	Unconditioned nursery (1923–25)— natural humidity		Cond	itioned nu	After discharge to general wards (1926–29)— natural humidity			
Weight at begin- ning of each week			Low relative humidity (25–49 percent)				High relative humidity (50–75 percent)	
(10.)	Number of cases	Average weekly gain (oz.)	Number of cases	Average weekly gain (oz.)	Number of cases	Average weekly gain (oz.)	Number of cases	A verage weekly gain (oz.)
$\begin{array}{c} 1.5-1.9, \\ 2.0-2.4, \\ 2.5-2.9, \\ 3.0-3.4, \\ 3.5-3.9, \\ 4.0-4.4, \\ 4.5-4.9, \\ 5.0-5.4, \\ 5.5-5.9, \\ 6.0 \ \text{and over} \end{array}$	$egin{array}{c} 0 \\ 1 \\ 26 \\ 44 \\ 49 \\ 55 \\ 51 \\ 39 \\ 33 \end{array}$	$\begin{array}{c} -7.0 \\ 1.6 \\ 3.2 \\ 2.9 \\ 4.3 \\ 4.3 \\ 5.6 \\ 5.8 \\ 3.6 \end{array}$	$egin{array}{c} 3 \\ 5 \\ 13 \\ 13 \\ 14 \\ 26 \\ 27 \\ 18 \\ 10 \\ 8 \end{array}$	$\begin{array}{c} 2.7\\ 1.0\\ 1.1\\ 2.8\\ 3.9\\ 3.0\\ 3.4\\ 5.9\\ 6.9\\ 6.6\end{array}$	$1 \\ 9 \\ 23 \\ 48 \\ 84 \\ 103 \\ 103 \\ 63 \\ 31 \\ 15$	0, 2 2, 8 3, 4 4, 1 4, 5 5, 4 5, 0 5, 0 4, 7	14 35 20 31	

shows the average gain in weight per week of premature infants of specified weights in the unconditioned nursery, the air-conditioned nurseries under low humidity, and the air-conditioned nurseries under high humidity, and of infants in the general wards who had been discharged from the air-conditioned nurseries of the hospital. "The data included all infants [of these weights] treated in the nurseries between 1923 and 1929 except those dying from nonpreventable diseases and those dying within the first 48 hours after admission. The gains in weight have not been corrected for the initial loss of weight or for any other loss resulting from vomiting, diarrhea, and febrile periods."

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The authors comment (p. 1204) "that the gain in weight is comparatively small among the patients in the lowest weight groups and that it increases progressively as the infants grow larger." For infants weighing less than 5 lb. (2,268 gm.) "the gain in weight is greater under high than under low humidity," but "the reverse holds true for patients in the groups weighing more than 5 lb. . . . When a premature infant reaches a weight of 5 lb. his physiologic functions are adequately stabilized, subcutaneous fat has increased, the sweat glands respond normally, and he therefore requires an environment more or less comparable to that of the full-term infant."

Effect of type of feeding

The effect of type of feeding on growth in weight of premature infants has been studied by Gordon, Levine, and McNamara (44). Their series consisted of 122 healthy white premature infants (weighing at birth 1,022 to 1,996 gm.) on three types of milk feeding: pooled unmodified human milk (16 infants), evaporated whole milk with added carbohydrate (39 infants), and a powdered half-skimmed cow's milk mixture with added carbohydrate (67 infants). The increase in weight during the period from 7 to 28 days after birth was recorded. The daily gain in weight per kg. of body weight among the group as a whole was significantly larger for the infants fed half-skimmed cow's milk (15.7 gm.) and evaporated milk (14.1 gm.) than for those fed human milk (12.5 gm.). Among the smaller infants (less than 1,621 gm., the mean birth weight) the difference in rate of gain was striking-17.3 gm. daily for those receiving half-skimmed cow's milk (31 infants) compared with 11.7 gm. for those receiving human milk (4 infants). Among the infants weighing more than 1,621 gm. the differences were not significant. (See also Nutrition, p. 169.)

Growth of head and thorax

PRENATAL GROWTH OF THE HEAD

In fetal life the growth of the head proceeds at a very rapid rate, which is greater in the earlier than in the later 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. (See fig. 9.)

Ylppö (107, pp. 174–175) states that in premature children the growth of the head is relatively the least retarded compared with growth of the thorax, growth in weight, and growth in length. "The growth of the head in premature children seems to follow its own rather independent laws without as a rule being very dependent on the bodily development."

Measurements of the head in relation to gestational age, crown-heel length, and birth weight are somewhat meager. Head measurement is important to establish criteria for determination of fetal age; for diagnosis of abnormal conditions, such as hydrocephalus and microcephalus; and for consideration in obstetric practice of head size in relation to size of pelvic outlet. The measurements of the head that are particularly useful from a clinical standpoint are the occipitofrontal diameter and circumference.



Figure 9.—The changes in body proportions in fetal life (from Stratz, C. H.: Wachstum und Proportionem des Fötus. Ztschr. f. Geburtsh. u. Gynäk. 65: 36, 1910).

Occipitofrontal diameter and body length

Scammon and Calkins (86) have reported the occipitofrontal diameters of the heads of 369 dead fetuses and infants according to body length. The observed diameter as well as that calculated to allow for the effect of birth molding and of preservation are shown in table 35.

The differences between the observed means and the calculated means are very slight except for 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 35), Scammon and Calkins report 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.

To exclude the influence of birth molding on the measurements Scammon and Calkins present figures for length and head diameter of 5 live-born premature and 27 full-term infants whose heads were not molded because they were delivered by cesarean section or by breech extraction "easily performed." The 5 infants were premature "according to the menstrual history and the body length." Individual data for these infants and averages for the 27 full-term infants are shown in table 36.

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		Occipitofrontal diameter (cm.)					
Mean crown-heel length (cm.)	Number of cases	Observed range		Observed	Calculated		
		Maximum	Minimum	mean	mean		
3.72 7.54 12.42 17.28 22.63 27.21 32.39 37.06 42.36 47.14 52.34	17 29 45 28 52 46 36 36 29 24 24 27	$\begin{array}{c} 1.8\\ 2.7\\ 3.9\\ 5.1\\ 6.8\\ 7.8\\ 9.0\\ 10.1\\ 11.5\\ 12.3\\ 12.9\end{array}$	1.0 1.4 2.6 3.8 4.8 6.0 7.1 7.9 8.7 9.9 10.5	$\begin{array}{c} 1.37\\ 2.17\\ 3.32\\ 4.47\\ 5.79\\ 6.92\\ 8.00\\ 8.88\\ 9.99\\ 10.92\\ 11.72\end{array}$	$\begin{array}{c} 1.\ 27\\ 2.\ 17\\ 3.\ 32\\ 4.\ 46\\ 5.\ 69\\ 6.\ 86\\ 8.\ 01\\ 9.\ 11\\ 10.\ 35\\ 11.\ 48\\ 12.\ 70\end{array}$		

 TABLE 35
 Occipitofrontal diameter of head and crown-heel length; 369 dead fetuses and infants (Scammon and Calkins)

 TABLE 36
 Measurements of unmolded heads of living newborn infants (Scammon and Calkins)

Infants	Sex	Age (hours)	Method of delivery	Crown- heel length (cm.)	Occipito- frontal diameter of head (cm.)	Occipito- frontal circumfer- ence of head (cm.)
Premature infants: 1 2 1 3 4 5 A verage for 27 newborn infants	M M M F F	29 28½ 1 2 8½	Breech Post. Cesarean Breech. do.	39.4 39.6 47.0 47.5 47.5 50.5	10. 1 9. 6 11. 1 11. 6 11. 2 12. 2	29. 0 27. 2 32. 6 32. 4 32. 0 35. 2

¹ The author notes that infant No. 2 was dead.

Occipitofrontal diameter and body weight

Clifford (25), who believes that the occipitofrontal diameter can be measured with considerable accuracy from roentgenograms of the fetal head in utero, concludes from a study of 479 infants: "In the group of infants of greatest interest from the point of view of their degree of maturity, a close relationship was found to exist between body weight and occipitofrontal diameter. . . . In the series investigated, all infants with an occipitofrontal diameter of less than 10 cm. were found to weigh less than 4 lb. (1,800 gm.). Those with the diameter between 8 and 9 cm. were found to weigh less than 3 lb. (1,360 gm.). Those whose diameters were below 8 cm. were all nonviable." Ince (49), however, on the basis of the birth weights and head diameters of 1,010 infants, concluded that "the range of variation in . . . the occipitofrontal diameter of the fetal skull is too great to allow an accurate estimation of either the birth weight or the maturity in any given case, although it will give a rough guide to the average weight and maturity." His series included only 28 observations on infants with a birth weight of less than 5 lb. (2,268 gm.).

Occipitofrontal circumference and body length

The figures of Scammon and Calkins (86, p. 93) for observed and calculated head circumference of 367 dead fetuses and infants of specified mean crown-heel lengths are shown in table 37.

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Physical Growth of Premature Infants

		Occipitofrontal circumference (cm.)					
Mean crown-heel length (cm.)	Number of infants	Observed range		Observed	Calculated		
		Maximum	Minimum	mean	mean		
3.66 7.54 12.42 17.28 22.53 27.31 32.39 36.99 42.32 47.14 52.34	16 29 45 28 52 46 36 35 29 24 27	4. 9 7. 6 11. 3 14. 6 19. 4 22. 5 26. 1 29. 3 31. 2 36. 4 37. 3	$\begin{array}{c} 2.\ 6\\ 4.\ 2\\ 7.\ 6\\ 10.\ 7\\ 14.\ 2\\ 17.\ 3\\ 20.\ 4\\ 23.\ 5\\ 28.\ 8\\ 32.\ 0 \end{array}$	$\begin{array}{c} 3.\ 75\\ 6.\ 19\\ -9.\ 56\\ 13.\ 18\\ 16.\ 71\\ 19.\ 98\\ 23.\ 26\\ 26.\ 02\\ 29.\ 06\\ 32.\ 29\\ 34.\ 85\\ \end{array}$	$\begin{array}{c} 3.\ 77\\ 6.\ 39\\ 9.\ 68\\ 12.\ 96\\ 16.\ 51\\ 19.\ 73\\ 23.\ 16\\ 26.\ 27\\ 29.\ 87\\ 33.\ 12\\ 36.\ 63\\ \end{array}$		

TABLE 37	Occipitofrontal	circumference	of the hea	d and	crown-heel	length;	367
	dead fetuses and	infants (Scan	nmon and (Calkins	5)		

In Scammon and Calkins' measurements of head circumference, as in those of head diameter, the observed and calculated means show relatively small differences except as birth molding affects the head measurements of the more mature infants. For an average body length at birth of 50.2 cm. (not shown in table 37), the authors report an average head circumference of 32.4 cm. for "fresh dead" infants, 35.0 cm. for infants with unmolded heads, and 35.2 cm. as calculated to allow for molding. They comment (**p. 95**) that their figures for head circumference are slightly higher than those usually reported, partly because the body length of 50.2 cm. is slightly greater than the usual figure but largely because they have made allowance for molding.

Table 36 shows the figures of Scammon and Calkins for the head circumference of 5 premature infants and the average for 27 full-term infants delivered by cesarean section or by breech extraction "easily performed," so that the heads were not molded during birth.

Occipitofrontal circumference and body weight

The figures of Reiche (79) and of Ylppö (108) for head circumference at birth of premature infants according to birth-weight groups are shown in tables 38 and 39. Reiche also shows average length of specified numbers of infants in each weight group, and Ylppö shows for comparison the average head circumference at birth of a group of full-term infants.

THE THORAX AT BIRTH

The average circumference of the thorax at the nipple line in mature newborn infants is stated by Taylor (99) to be 32.3 cm. for males and 32.1 cm. for females. Scammon and Rucker (87) have pointed out that the size of the thorax varies as the degree of aeration of the lungs changes. For example, they found that 15 minutes after birth the average circumference at the nipple line was 31.2 cm.; that 12 hours after birth it was 30.7 cm.; and that on the twelfth day after birth the measurement of 31.2 cm., that of 15 minutes after birth, was again attained. The smallest circumference (29.7 cm.) was found on the third day after birth. The exact ages at which the measurements of newborn infants were made in the several series to be discussed are not known. Ylppö (108) gives figures for the circumference of the thorax of premature newborn infants according to birth weight as shown in table 39. He found that the average circumference of the thorax of full-term infants (weight 3,000-3,500 gm.) was 31.0 cm. The average circumference of the premature infant's thorax varied between 20.8 and 29.5 cm., depending on the degree of prematurity.

The averages for thorax circumference of premature infants found by Reiche (79, p. 348) ranged from 22.5 to 28.4 cm. (See table 38.)

TABLE 38Average length, average head and thorax circumference, and ratio of
thorax to head circumference at birth, by birth-weight groups; 88
premature infants (Reiche)

Birth weight group (gm.)	Number of infants	A vorago	Average	Circumference of thorax		
		A verage length (cm.)	circumfer- ence of head (cm.)	A verage (cm.)	Percent of head cir- cumference	
800-1,200 1,200-1,500 1,500-2,000 2,000-2,500	12 26 28 22	37. 4 41. 6 44. 2 46. 5	26. 8 28. 4 30. 3 32. 2	22. 5 24. 8 27. 2 28. 4	84. 0 87. 3 89. 8 88. 2	

¹ Calculated from Reiche's figures.

TABLE 39Average head and thorax circumference and ratio of thorax to head
circumference at birth, by birth-weight groups; 243 premature and
100 full-term infants (Ylppö)

		A verage	Circumference of thorax		
Birth-weight group (gm.)	Number of infants	circumfer- ence of head (cm.)	Average (cm.)	Percent of head cir- cumference	
1,000 or less	16 78 75 74	25. 0 31. 8 30. 0 32. 3	20. 8 24. 5 26. 3 29. 5	83. 2 77. 0 87. 7 91. 3	
3,000-3,500	100	33. 5	31.0	92.5	

He comments: "The fetal development of the chest is of great importance for the premature child's ability to survive; children with a chest circumference of less than 21 cm. are not able to survive; those with a chest circumference of less than 23 cm. still have a doubtful prognosis."

RELATION OF THORAX TO HEAD CIRCUMFERENCE AT BIRTH

It is generally recognized that disproportion between the circumference of the head and that of the thoax is a sign of prematurity which is more reliable than either measurement alone. Taylor (99) found that the average thorax circumference of 125 full-term male infants was 93 percent, and that of 125 full-term female infants 94 percent, of the average head circumference; and measurements by Zeltner (110) of 516 full-term infants yielded a corresponding percentage of 94. Ylppö (108) found this percentage to be 92.5 in 100 full-term infants. Among the 243 premature infants measured by Ylppö, on the other hand, the percentage ranged from 83.2 in the lowest to 91.3 in the highest of the four weight groups studied, though the disproportion was greatest (77.0 percent) in the weight group 1,001 to 1,500 gm. (See table 39.) Similar percentages calculated from the measurements by Reiche (79) of 88 premature infants (table 38) also show this disproportion in all four weight groups, with the greatest difference between head and thorax in the smallest infants.

Instead of the ratio of thorax circumference to head circumference used by Ylppö, Zeltner (110) reports the relation between the two measurements as the excess of average head circumference over average thorax circumference, together with the percentage of infants in each of six birth-weight groups in whom the excess was greater than a specified amount. He took various measurements of 700 premature infants and 694 full-term infants who were under clinical observation in the Infants Home of Nürnberg in 1919-35. Table 40 shows the amounts by which Zeltner found head circumference to exceed thorax circumference at birth, by birth-weight groups ranging from 1,000 to 1,500 gm. to 4,000 gm. or more, together with the percentage of infants in each group in whom the excess in head circumference was 4.0 cm. or Zeltner notes that among the full-term newborn infants (516) more. for whom these measurements were taken this difference averaged 2.13 cm. but that among the premature infants (presumably 700, since no other figure is given) the average difference ranged from 3.45 to Both the average excess in head circumference and the 4.07 cm. percentage of cases in which the excess was 4 cm. or more were highest in the lowest weight group (4.07 cm. and 55.1 percent of the cases), and both the excess and the percentage decreased progressively with each higher birth-weight group until in the birth-weight group 4,000 gm. or more they had reached the low figures of 0.7 cm. and 3.3 percent.

TABLE 40Excess of average head circumference over average thorax circumference
at birth, by birth-weight groups; 700 premature and 516 full-term
infants (Zeltner)

Birth-weight group (gm.)	Excess of average head circumference over average thorax circum- ference (cm.)	Percentage of cases in which head circum- ference was at least 4 cm. more than thorax cir- cumference
1,000-1,500 1,500-2,000 2,000-2,500 2,500-3,000 3,000-4,000 3,000-4,000 4,000 or more	4.07 3.57 3.45 2.70 1.60 0.70	55. 1 51. 8 43. 9 27. 0 14. 4 3. 3

POSTNATAL GROWTH OF THE HEAD

The available studies on postnatal growth of the head in premature infants have been reviewed by Meredith (61, p. 44) as follows:

"Data for head circumference on infants born prematurely are available from Mohr and Bartelme [64] and from Talbot [98]. In Talbot's study 'the criteria used in establishing prematurity were weight, stature, and general considerations, such as facies, texture of the skin, undeveloped nails, cry, unstable temperature, and history of expected birth'; Mohr and Bartelme's criterion was 'birth weight less than 2,500 gm.' Talbot's subjects were considered 'from 4 to 10 weeks premature'; Mohr and Bartelme's had a mean gestation period of approximately 34 weeks. Talbot used statutory age; Mohr and Bartelme corrected statutory age for the estimated amount of prematurity. Talbot's data afford a mean 1 month after birth; Mohr and Bartelme's data supply means at older ages. [Table 41] aligns both studies with comparable materials on full-term infants.

"It will be seen that:

- "1. At the end of the first postnatal month, the mean head girth of the premature infants studied by Talbot is 30.9 cm. (12.2 in.)—roughly equivalent to the mean head girth for normal fetuses 1 month prior to birth. The mean for North American full-term infants age 1 month is higher by 5.7 cm. (2.2 in.).
- "2. At the middle of the second postnatal year the mean head girth of the premature infants followed by Mohr and Bartelme is practically equal to that for full-term infants. (Adjustment of the premature means at 18 months to statutory age would only reduce it from 47.9 cm. to 47.6 cm.) It will be recalled that Mohr and Bartelme's subjects were the recipients of excellent postnatal care.

 TABLE 41
 Mean head circumference of premature and of full-term infants at specified ages (Meredith)

	Infants bo tur	orn prema- ely	Full-term	Prematurely	
Age (months)	Number	Mean head circumfer- ence (cm.)	Number	Mean head circumfer- ence (cm.)	less than full-term)
1	$ \begin{array}{r} 13 \\ 6 \\ 10 \\ 15 \\ 16 \\ 48 \\ 48 \end{array} $	30. 9 1 37. 3 42. 0 44. 2 45. 9 47. 6	195 1, 239 2, 193 1, 791 2, 166 1, 611	36. 6 39. 9 43. 0 44. 9 46. 0 47. 6	5.7 2.6 1.0 .7 .1 0

¹ The means for premature infants at ages 3 to 18 months represent statutory age minus the estimated amount of prematurity.

"The generalization which accrues is that the mean trends for head circumference of infants born 'prematurely' and 'at term' gradually converge during infancy. In relation to the trend for full-term infants, the trend for premature infants ascends from a lower level at birth to become almost superimposed by the middle of the second year."

RATIO OF THORAX TO HEAD CIRCUMFERENCE AFTER BIRTH

Comparative measurements of head and thorax were taken by Zeltner (110) for varying numbers of premature and full-term infants during the first 6 months of life. As table 42 shows, the disproportion noticeable at birth tended to disappear except in the lowest weight group, and even in this group the excess in head over thorax measurement at 6 months of age (2.20 cm.) had decreased to about the figure for the

TABLE 42 Relative growth of head and thorax in the first 6 months of life among premature infants of specified birth weight and among full-term infants (Zeltner)

	gm.	Excess (cm.)	2.13	2.31	-0.21
- Birth-weight group	More than 2,500	Thorax (cm.)	32.78	37.36	42.42
		Head (cm.)	34.91	39.67	42.21
	00-2,500 gm.	Excess (cm.)	3.45 3.12	1.37	0.30 0.30
		Thorax (cm.)	28. 74 30. 74	33.95 36.42 37.60	30.00 90.00
	2,	Head (cm.)	32. 19 33. 86	36.04 37.79	39.30 40.80
	1,500-2,000 gm.	Excess (cm.)	3.57	3.00 2.30 2.30	0.90
		Thorax (cm.)	26.35 28.65	31.18 34.01 36.10	30.60 39.60
		Head (cm.)	29.92 32.02	34.18 36.40 37.60	39.68 39.68
	1,000-1,500 gm.	Excess (cm.)	4.07 4.21	3.04 9.93 9.94	531 531 531 531 531 531 531 531 531 531
		Thorax (cm.)	23. 93 24. 79	27.88 31.13 34.90	34.50 36.80
		Head (cm.)	28.00 29.00	32.07 34.17 36.80	39.00 39.00 39.00
	Age		Birth 1 mo	2 mo. 3 mo.	5 mo 6 mo

Physical Growth of Premature Infants

full-term infant at birth (2.13 cm.). Zeltner (**p. 105**) concludes that an excess at birth of 3.45 cm. or more has no negative effect on the development of premature infants but is only one of the evidences of prematurity.

Summary

In prenatal life growth of all parts of the body does not proceed at the same rate; for example, some parts may be still in the embryonic stage while others are in the fetal stage of growth. The changes that occur at different stages of development are not sharply differentiated and fetal development of some parts of the body extends into the neonatal period.

Studies of body form and organ development show that at about the twenty-eighth week of intrauterine life the fetus has reached the stage at which extrauterine life should be possible.

PRENATAL GROWTH IN WEIGHT AND LENGTH

Growth of the fetus in weight and length at different stages of development has been determined necessarily by measurements of dead fetuses. Reports of measurements vary considerably because of differences in technique, methods of analyzing the data, and the small numbers of infants studied at different stages of development.

The earlier data (before 1915) most often quoted are from German sources. Ylppö (1919) presented material on fetal growth based on averages of the data from some of these earlier studies. He showed the average weight and length at each lunar month from the first to the tenth. The percentage increase in weight was greatest in the third month (779 percent) and then decreased sharply each month up to the eighth month, when it was 43, decreasing to 39 in the ninth month and to 34 in the tenth. In crown-heel length the percentage increase, starting from 300 in the second month, also decreased sharply each month to 18 in the seventh month, and then more gradually to 11 in the tenth month.

Ylppö pointed out that deviations from these normal curves of growth were considerable in individual cases.

⁻ The chief North American sources of data on fetal growth are the studies of Mall, Streeter, and Scammon and Calkins.

Mall and Scammon and Calkins give increases in crown-heel length and Streeter for crown-rump length which in monthly percentages of increase are in approximate agreement at and after the sixth lunar month and are similar to Ylppö's figures after the sixth month. They show a decrease in percentage gain in each month. At the ninth lunar month, which might be considered the upper limit of prematurity, the average crown-heel measurement is given by Mall as 47.0 cm. and by Scammon and Calkins as 45.7 cm. Ylppö reported 45.0 cm.

The figures for fetal weight presented by Streeter and by Scammon and Calkins differ rather widely at each lunar month. In both reports, however, as in Ylppö's, the rate of gain was found to be very great in the earlier months and to decrease rapidly in the earlier and more gradually in the later months. The average weight at the ninth lunar month was found by Streeter to be 2,478 gm.; by Scammon and Calkins, 2,208 gm. Mall did not report on weight. Streeter calls attention to the fact that the amount of gain in length shows strikingly little variation from month to month, while the amount of gain in weight increases as strikingly.

POSTNATAL GROWTH IN WEIGHT AND LENGTH

Most of the information on growth of premature infants in the earlier months after birth is based on European studies. Data from North American sources are meager. The data in some of the studies are somewhat unsatisfactory because many of the factors that are now known to influence growth in addition to birth weight, such as race, sex, and certain environmental and nutritional factors, have not been given consideration. In addition, techniques of measurements and methods of analyzing data have varied widely in different studies.

Among the important European sources of growth data are those of Ylppö and Zeltner. Ylppö compared his data on extrauterine growth with data on intrauterine growth that he compiled from various sources. He concluded that premature infants tend to follow the laws of growth corresponding to their conceptional age. He found, however, that the growth of premature infants was distburbed at first by extrauterine existence and considered that nutritional factors (including rickets) probably were largely responsible.

Zeltner studied growth of premature infants in 3 birth-weight groups; those weighing less than 1,000 gm. were not considered. He reported average actual increases per month through the ninth month for 700 premature infants compared with full-term infants. He found that birth disturbed the intrauterine growth rate in weight and length in each of the birth-weight groups, particularly the lowest one. From the second through the sixth postnatal month, however, he showed monthly increases in weight that were greater for premature infants than for full-term infants.

In the North American literature the studies reported are those of Scammon, Mohr and Bartelme, Blackfan and Yaglou, and Gordon and his coworkers. Scammon reported average percentage increases in weight for 9 postnatal months for 78 infants in 3 birth-weight groups, compared with published data for full-term infants. Like Zeltner, he found that growth was disturbed in the first postnatal month. He also found that the percentage increment in weight was largest in the second month and decreased gradually thereafter. These increments were found to be inversely proportional to the birth weight. He concluded, as did Zeltner, that during the period covered the growth tendency in premature infants is in general that of fetuses of the same size and age rather than that of full-term infants.

Mohr and Bartelme give figures for average weight and height of a small number of prematurely born white boys and girls at 3-month intervals during the first year of life and for a somewhat larger number at 18 months of age.

Blackfan and Yaglou reported average growth in length and weight of premature infants in relation to atmospheric conditions. The growth in length per month for 3 months was studied according to fetal age among infants in the air-conditioned nurseries. It was found to proceed at a markedly slower rate than during intrauterine life. The actual increases in length for infants of all fetal ages were found to be greater in the second month than in the first and in the third month than in the second. The infants of gestational age under 7 months showed more rapid increases in length than those of higher gestational age. The data for growth in weight were analyzed by Blackfan and Yaglou according to the weight at the beginning of each week of observation. Average weekly gain in weight in unconditioned nurseries was compared with that in conditioned nurseries with low and with high relative humidity. The gain in weight among the infants weighing less than 5 lb. was greater when the relative humidity was high, while among those weighing 5 lb. or more the reverse was true.

Gordon and his coworkers found that the rate of growth in weight of healthy white premature infants is influenced by dietary factors when conditions of environment and care are held constant. Those infants fed human milk showed a smaller mean daily gain in weight than those fed evaporated milk or those fed half-skimmed cow's milk. The differences were found to be more marked in the smaller infants.

GROWTH OF HEAD AND THORAX

Growth of the head proceeds at a very rapid rate, especially during embryonic and early fetal life. Measurements of the head, particularly the occipitofrontal diameter and circumference, are useful to determine the maturity of the infant; to diagnose abnormal conditions such as hydrocephalus and microcephalus; and for obstetric purposes (relation of head circumference to pelvic outlet). Determinations of prenatal growth of the head are somewhat meager.

Scammon and Calkins give mean occipitofrontal diameter and circumference of the head for each 5 cm. of mean crown-heel length from about 8 to 52 cm. For a fetus measuring 47 cm. the observed head diameter ranged between 9.9 and 12.3 cm., the observed mean was 10.92 cm., and the mean calculated to allow for birth molding was 11.48 cm. The corresponding figures for head circumference were 28.8 to 36.4 cm., 32.29 cm.. and 33.12 cm.

A relationship between weight and the diameter of the fetal head in utero, measured by means of roentgenograms, is shown, according to Clifford, by his series in which infants with a diameter of less than 10 cm. weighed less than 4 lb. and those with a diameter between 8 and 9 cm. weighed less than 3 lb.

Ylppö and Reiche give figures for average circumference at birth of the heads of premature infants by birth-weight groups. In the highest weight group (2,000–2,500 gm.) their figures for head circumference are almost identical (32.3 and 32.2 cm.); for this group Reiche gives average length as 46.5 cm.

The circumference of the thorax measured on living infants in the early neonatal period has been found to vary with the degree of aeration of the lungs, but the measurements in the studies cited are those of "newborn" infants without reference to this factor. The average circumference in Ylppö's series of premature infants ranged from 20.8 to 29.5 cm., depending on the birth weight; the latter figure compares with Reiche's 28.4 cm. for the highest weight group. The thorax circumference for full-term infants is given by Taylor as 32.3 cm. for males and 32.1 cm. for females.

More important as a criterion of prematurity than either head circumference or thorax circumference alone is the relation between the two. In full-term infants the average circumference of the thorax has been found to be 93 to 94 percent of the average head circumference. In premature infants the percentage is much lower, ranging from 83.2 percent for infants of 1,000 gm. or less (Ylppö) and 84.0 percent for infants of 800 to 1,200 gm. (Reiche) to 88.2 percent (Reiche) and 91.3 percent (Ylppö) for infants of 2,000 to 2,500 gm. Zeltner reports excess of average head circumference over average thorax circumference ranging from 4.07 cm. in the birth-weight group 1,000 to 1,500 gm. to 3.45 cm. in the group 2,000 to 2,500 gm., compared with 2.13 cm. for full-term infants.

Two North American studies reporting measurements of the heads of living premature infants show that the head circumference of premature infants gradually converges with that for mature infants by the middle of the second year.

According to Zeltner, the average head and thorax circumferences of premature infants at 6 months of age were less than those of fullterm infants by amounts that were inversely proportional to the birth weight. Except in the smallest group (1,000–1,500 gm.), however, the disproportion between thorax and head circumference had practically disappeared.

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PROGNOSIS FOR PREMATURE INFANTS

It is of the greatest importance not only to know the chances for survival of premature infants in the neonatal period but to have evidence in regard to their future development—physical, mental, and emotional.

Percentage of premature infants that survive

Studies of hospital statistics have shown that the percentage of deaths among premature infants (those weighing 2,500 gm. or less at birth) is inversely proportional to the birth weight and that, in different hospitals, there are rather wide variations in these fatality rates (deaths per 100 premature infants) within each of the 4 standard birth-weight groups. (See p. 41.) It would be expected that the chances of survival would also be directly proportional to the quality of care given. With a view to discovering such a relationship the percentage of survival among premature infants in recent years has been compared with that of earlier years in certain hospitals that have made definite efforts to improve their care of premature infants.

Reports from 12 hospitals caring for 12,651 premature infants within the period 1922-40 and from 6 hospitals caring for 5,731 premature infants within the period 1940-45 were compiled to show changes in fatality and survival percentages in the two periods. The lowest birth-weight group (less than 1,000 gm.) does not lend itself to statistical discussion, as only about 5 percent of the premature infants born alive are in this group and almost all of them die. In each of the three higher birth-weight groups, the variation in fatality rates among the individual hospitals was confined within a much narrower range in the later period and the rates in general showed marked decreases. (See table 19.)

Four of the hospitals reported fatality rates for both an earlier and a later period, and these were hospitals in which special attention has been given in recent years to care of premature infants. Their comparable figures for the earlier and later periods therefore afford opportunity for sharper definition of the relation between quality of care and survival. Table 43 gives, for each of these hospitals, the percentages of premature infants that survived in the three birthweight groups in the later compared with the earlier period.

In all four hospitals there was marked improvement in the percentages of infants surviving in the later period. The improvement was greatest in hospital 3; this hospital and hospital 4 showed improvement in all three weight groups. For hospital 1 the percentage was the same (50.0) in the two periods for the weight group 1,000

Prognosis for Premature Infants

	1,000–1,500 gm.		1,501-2,000 gm.		2,001–2,500 gm.	
Hospital and periods covered	Earlier	Later	Earlier	Later	Earlier	Later
	period	period	period	period	period	period
1 (1922-39 and 1940-45)	50. 0	50. 0	78. 4	85. 6	89. 0	92. 8
2 (1935-40 and 1943-45)	45. 9	53. 3	76. 9	87. 2	95. 9	95. 6
3 (1924-39 and 1940-45)	33. 7	58. 6	58. 9	81. 7	89. 7	95. 4
4 (1926-40 and 1941-45)	36. 8	51, 2	75. 1	83. 2	94. 2	95. 8

 TABLE 43
 Percentages of survival among premature infants in specified earlier and later periods, by birth-weight groups; 4 hospitals

to 1,500 gm. For hospital 2 there was an insignificant reduction (from 95.9 to 95.6) in the later period in the weight group 2,001 to 2,500 gm., but for this hospital the earlier percentage of survival was already high.

These figures lead to the conclusion that under good conditions of care the prognosis for survival of premature infants in the three higher birth-weight groups may be assessed as follows:

Weight group (gm.)	Percent survival	Prognosis
2,001-2,500	At least 93	Excellent.
1,501-2,000	At least 82	Good.
1,000-1,500	At least 50	Fair.

Physical development

In studies of growth there are two methods of approach: (1) longitudinal studies, or measurements of weight and length of individual infants made at intervals over a period of time, and (2) group studies based on averages of the weights and lengths of infants at different ages. In the studies reported the averages at each age level are not always based on measurements of the same infants.

Before discussing the results of such studies it must be admitted that no entirely satisfactory norms for growth of premature infants have been established. Additional data need to be collected in order to answer the primary question of the expected rate of growth of a premature infant of a given birth weight from birth to the period at which the infant may be considered mature. In such studies the reliability of the results will be affected by certain factors mentioned on page 64.

There have been a number of long-term studies of the physical growth of premature children, which have been based largely on European infants. Only a few studies have been reported in the North American medical literature.

LONGITUDINAL STUDIES

Ylppö (107) in 1919 reported repeated weights and measurements of 700 premature infants in four birth-weight groups. The weights and measurements were taken on the largest proportion of the infants during the first year; on a smaller proportion during the second year; and in one instance up to the age of 9 years, calculated from the date of conception.

Ylppö concluded (p. 173) that with few exceptions the growth of premature infants with birth weights of 2,500 gm. or less shows a

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marked disturbance in the first 3 to 5 years of life. He found that the weight and length of nearly all the premature infants remained lower during this period than the weight and length that he accepted as normal for children of equal conceptional age who were mature at birth, and the delay in growth among the premature children was greater the smaller the weight and length at birth. Ylppö notes (p. 165) that his conclusion that gain in length is affected in about the same way as gain in weight is contrary to "the prevailing opinion."

The disturbance in growth in Ylppö's series (p. 173) began immediately after birth and was proportionally greatest between the sixth and the twelfth postnatal month. In the conceptional age 2 to 4 years the premature infants began to catch up to the norms, and most of them had done so at about the conceptional age of 5 or 6 years. From this period on the weight and length curves of the premature children corresponded with those of full-term children, except that the recovery of the smallest prematures (birth weight less than 1,000 gm.) appeared not to be completed in this period.

Retardation in growth of the thorax (p. 174) lasted on the average a shorter time—to the conceptional age of 3 years—than retardation in



Figure 10.—A premature infant, 1 year old, weighing 20 lb. 13 oz., who weighed 2 lb. 8 oz. at birth (courtesy New York Journal American).

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Figure 11.—A premature infant, 5 months old, weighing almost 9 lb., who weighed 1 lb. 11 oz. at birth (courtesy Michigan Department of Health).

weight and in length. The growth of the head was the least retarded. In spite of many individual differences, therefore, Ylppö regarded it as "demonstrated" (p. 175) that immaturity itself and the associated factors for which it is responsible have as their almost inevitable consequence this temporary deviation of premature infants from the laws of growth determined by each individual's heredity. He attributed this retardation primarily to undernutrition and rickets and secondarily to infections, unsatisfactory functioning of the endocrine glands, and the inertness that deprives premature infants, especially the smaller ones, of "the growth-promoting stimulus of active movements."

Peiper (71), who reviewed the studies of growth of premature infants, comments that if Ylppö was correct in ascribing the retardation in growth mainly to undernutrition and rickets, it should be possible now with better knowledge of nutrition and "more effective means of defense against rickets," largely to overcome this handicap.

GROUP STUDIES

Mohr and Bartelme (64) made a long-term group study based on 477 examinations of 250 premature male and female white children born between 1922 and 1933 and on 173 examinations of 150 of their siblings. The age at examination was the chronological age corrected for the degree of prematurity. The authors took weights and measurements at 3, 6, 9, 12, 18, and 24 months of age and at yearly intervals up to 7, 8, and more years. As the figures are presented by sex and by birth-weight groups, the number of examinations at each age period is small, especially for the youngest and the oldest children. The authors considered, however, that they had made sufficient examinations of children from 1 to 7 years, inclusive, to insure reliable conclusions.

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In regard to weight Mohr and Bartelme concluded that—

- 1. As among full-term children, the prematurely born boys weighed more at birth than the prematurely born girls.
- 2. The prematurely born boys consistently weighed less than their full-term brothers until the age of 4 years was attained. They weighed less than the Woodbury "normal" weights for boys until the age of 3 years. After this they conformed fairly closely to the norms and to the weight curves of their siblings.
- 3. The prematurely born girls approximated the Woodbury measurements in weight between the ages of 9 and 12 months, after which they conformed fairly closely to these norms. No reliable difference was found between the mean weight of the girls and that of the sibling group.
- 4. Birth weight apparently influences the weight curves. Prematurely born boys and girls weighing 2,000 gm. or more at birth gained in weight relatively more rapidly and maintained a more rapidly increasing average weight than prematurely born children of the same sex weighing 1,500 gm. or less at birth.
- 5. Within the age range of the children in this series these children of smaller birth weights did not tend to reach the mean weights noted for the larger prematurely born children, the weight curves remaining persistently below those for the entire group and below those for siblings and Woodbury's norms.
- 6. The difference between the children of the larger and the smaller birth-weight group was distinctly greater among boys than among girls. Boys weighing 2,000 gm. or more at birth maintained their superiority in weight over the girls in this birth-weight group, whereas the weight curves of the boys and the girls in the birth-weight group 1,500 gm. or less were almost identical.

Slight differences were found in comparing the curves of growth in *length* for prematurely born boys and girls with their full-term siblings. The growth of the boys was somewhat more variable than that of the girls, and the siblings tended to excel the boys in stature until they were 3 years of age. The prematurely born boys also attained the Woodbury norms for boys at 3 years; the girls, at 18 to 24 months. Growth in stature, like growth in weight, was found to be influenced by birth weight. Boys, and to a lesser extent the girls, weighing 1,500 gm. or less at birth grew less rapidly in length than those of the corresponding sex weighing 2,000 gm. or more. The persistent, though slight, differences suggest, the authors believe, that the children in the smallest birth-weight group tend to remain somewhat shorter within the age range of the children studied.

In regard to *head circumference* Mohr and Bartelme found that-

1. Prematurely born boys as they grew older did not differ from their siblings in head circumference. Data for the girls on this point were not considered sufficient to warrant a conclusion. 2. The growth curves for head circumference for the smaller and the larger prematurely born children differed. For both sexes mean head circumference for children who weighed 1,500 gm. or less at birth remained consistently below the mean measurements for those weighing 2,000 gm. or more at birth.

The authors point out that their measurements of head circumference "do not indicate persistence of large head circumferences as a result of megacephalus observed among the prematurely born children."

A special study was made by Kunstadter and Bartelme (52) of the physical and mental development of 18 infants whose birth weight or lowest weight was less than 1,000 gm. Of the 13 children who were living at the time of the last examination (ranging at that time from $4\frac{1}{2}$ months to 6 years and 3 months in age) 7 were considered to be in good physical condition, 2 in fair condition, and 4 in poor condition. (For mental development of this group of children see p. 90.)

Mental and emotional development

Few long-term studies of the mental and emotional development of North American premature infants have been made, though from a clinical standpoint determination of mental and emotional development is of primary importance. An impression has been prevalent, which at least so far as mental development is concerned is not justified by recent studies, that the prospect is unfavorable. This impression is partly due to clinical judgments based on visits to physicians, after the neonatal period, of children with whom "there is something wrong," and it may have been strengthened by a well-known study on this subject, referred to later, based on unsatisfactory European case material and unsatisfactory methods of appraisal of mental status. Appraisals of the premature infant's mental development based on examination of American children by well-established objective tests suitable to their age give much more favorable results.

NORTH AMERICAN STUDIES

Studies by Gesell

In recent years techniques have been developed to test "developmental status," which, according to Gesell (40), "manifests itself in three major kinds of signs and symptoms: anatomic, physiologic, and behavioral." He regards behavior as "the most comprehensive and the most sensitive indicator of developmental status. . . Anatomic and physiologic criteria of growth and well-being can never be safely ignored or slighted; but they must always be correlated with the crucial criterion of behavior. The motor, the adaptive, the language, and the personal-social behavior of the child sums up most completely his capacity to grow." (For developmental scales for full-term infants, see appendix 3, p. 366.)

Gesell and his coworkers, whose methods for testing the developmental status of young infants are well established, have reported detailed studies of individual premature infants examined over a period

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of years in the Yale Clinic of Child Development. Gesell and Amatruda (42, pp. 290, 292) point out that the developmental status of the premature infant must always be appraised in terms of "corrected age" rather than postnatal age. (To arrive at the corrected age the number of weeks that the infant is premature is subtracted from the chronological age.) They regard it as a general truth that "prematurity in itself does not markedly alter the normal course of mental growth. It neither retards nor accelerates."

Gesell (39, p. 680) also briefly reviewed other studies and concluded:

"Present data, though scanty and sometimes contradictory, indicate that prematurity of birth in itself does not markedly distort, hasten, or retard the course of mental development, when the age of the infant is reckoned from conception. . . . Deviations, such as imperfect postural and locomotor control, are not necessarily permanent but frequently resolve in the first 2 years of life. . . . It is even suggested that in some instances the effects of intracranial hemorrhage may be overcome, possibly by substitutive or compensatory development. . .

"Prematurity carries with it numerous hazards which may inflict temporary or permanent penalty; but fortunately the infant is also protected by the inherent factors of organic maturation, which make for a normal course of mental growth."

Gesell (41, pp. 99, 100) says further:

"In the habit-forming field of personal-social behavior expressed in personality there may be skewing or discrepancy in his [the premature infant's] apparent favor. Such a personality discrepancy may assert itself with temporary vividness when a newborn full-term infant is compared with a preterm infant who has had 2 months of 'experience' in a socialized environment. All things considered, however, the extrinsic conditioning factors seem to be of secondary importance in determining the mental growth of the premature child. The substrate of maturation in cases without pathological complications is relatively secure and serves as a developmental safeguard for the prematurely born.

"The behavior of the premature infant is not alone a subject of scientific interest from a genetic standpoint; it is a subject of medical significance with direct and indirect bearing upon problems of child protection. Too frequently prematurity is not recognized by physician or nurse, and the child's welfare suffers in consequence. When more is known about the behavior characteristics of the premature there will be greater accuracy in diagnosing both the presence and the degree of prematurity. Refinements in the hygiene of the premature infant will also come through a better understanding of his behavior limitations and requirements."

Studies by Mohr and Bartelme and Kunstadter and Bartelme

The studies of Mohr and Bartelme (64) are in general agreement with Gesell's conclusions. These investigators made a survey of 250 white premature infants in families of "slightly inferior" socio-economic status cared for at the Premature Infant Station, Sarah Morris Hospital, Chicago. The age range for the group was $4\frac{1}{2}$ to 66 months; about one-sixth were in grade school. A control group of 152 full-term siblings of 124 of the children were also examined. The Gesell developmental schedule and the Stanford-Binet and Kuhlmann-Binet scales were used for estimating the intelligence of the children. The findings were as follows (*pp. 132–152*):

- 1. Comparisons of two groups of prematurely born children (those with siblings and the "total" group) with full-term children (siblings of prematurely born children) and standardization groups [Gesell and Binet norms] indicate that premature birth unassociated with intracranial injury does not affect mental development. . . .
- 2. If weight at birth and duration of the period of gestation are used as criteria, prematurity per se and degree of prematurity are not related to mental development, according to the mental tests here employed and within the age range tested. . . .
- 3. Comparison of mental growth of our prematurely born children who suffered intracranial hemorrhage at birth and those who did not . . . shows a tendency for the intracranial-hemorrhage group to be retarded.

Mohr and Bartelme (**pp. 201, 216**) also analyzed data on "habit formation and social adaptation" for the group of premature children whose physical and mental growth they studied. Their two sources of information were statements of the mothers (with notations on the clinical records of the children), which they considered of value as approximations, and the results of psychometric examinations, which are obviously more precise. Their conclusions follow:

"Our data would indicate that with respect to development of static functions the prematurely born group are able to sit unsupported at as early an age as the sibling group but are slightly delayed in walking. There is also a slight delay in the establishment of sphincter control, particularly among the boys. . . .

"We are unable to distinguish between the prematurely born group and the control sibling group with respect to earliest nursing and feeding habits. Apparently weaning from bottle feeding occurs at approximately the same time for both groups. Mothers tend to prolong breast feeding with prematurely born infants when they have the opportunity to do so, but our group was not generally nursed at the breast. The prematurely born group retains infantile sucking habits with greater frequency than the full-term group, but allowance must be made for the fact that the prematurely born group are younger and have had less time to overcome these habits.

"There appears some slight delay in the establishment of more independent habits of feeding; viz, prematurely born boys apparently are unable to drink from a cup without assistance as early as the boys of the sibling control group.

"In the establishment of speech the prematurely born girls evidence that relative precocity generally observed among normal children. Developmental histories indicate that on the average the prematurely born children talk at as early an age as the siblings. However, speech defects—particularly stuttering—are more common among our premature group.

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"Limited data available pertaining to relatively few children of our group who have reached school age indicate that the school attainment of the prematurely born children as a group is on a par with the group of full-term siblings. Those who are appreciably retarded in school attainment are among those who have suffered intracranial hemorrhage with consequent central-nervous-system damage.

"Prematurely born children are more frequently observed to evidence dependency reactions in relation to their mothers. Temper display occurs with distinctly greater frequency among the prematurely born children than among the sibling group. The full-term children are reported by their mothers to be somewhat more adequate in their earliest social responses; i. e., they are more frequently on good terms with their own siblings than are the prematurely born children, and it may be that this difference extends to contact with other children outside the home. The oldest full-term group are described as more self-reliant than the corresponding prematurely born group."

Benton (13, p. 733) comments:

"Among all the studies of mental development of prematurely born children, this investigation by Mohr and Bartelme must be accorded first rank in respect to excellence. Due attention is paid to the factor of socio-economic status, objective test scales are utilized for the estimation of the intelligence of the children, for comparative purposes a parallel investigation is done on a fairly adequate control group, and the authors evaluate their findings critically."

Of the 12 surviving infants in a group of 18 with a birth weight or low weight of less than 1,000 gm. whose mental development was tested by Kunstadter and Bartelme (52, pp. 230, 239), 2 were reported, at 2 years and 5 years of age, respectively, to be of superior intelligence; 6, ranging in age from $4\frac{1}{2}$ months to $6\frac{1}{4}$ years, of average intelligence (and in good physical condition); and 4, ranging in age from $5\frac{1}{2}$ months to 4 years, mentally retarded (and also in poor physical condition). Two infants in this group survived intracranial hemorrhage; one was physically and mentally retarded at 9 months and the other was well-developed physically and of high average intelligence at 2 years. A third infant who survived intracranial hemorrhage was not examined mentally but was reported "doing well" at an orphanage at 6 months of age.

Studies by Shirley

Shirley (90, pp. 347-359) reports the results of 215 developmental tests given to 63 children (27 boys and 36 girls) whose birth weights were less than 5 lb. Seventeen of these children had 5 tests and 16 had 4 tests at 3-month intervals from 6 to 18 months of chronological age. Twenty-three of the 63 children had tests at 24 months, but only 2 at 30 months. The test used was a modification by Cattell of the Yale developmental schedule. The premature infants were compared with norms based on tests of full-term infants and also with a control group of 250 full-term infants examined under similar conditions.

Compared with the test norms, the infants weighing less than 4 lb. at birth were retarded by a month or more throughout the 18-month period, but infants weighing 4 to 5 lb. at birth had reached these norms by 9 months of age. When compared with the control group, however, even the infants weighing 4 to 5 lb. at birth were a month retarded throughout the 18-month period. In connection with this finding it should be noted that the socio-economic status of the control group was stated by the author to be better in general than that of the premature group. The premature children were found to be "more retarded in manipulative development than in intellectual grasp and social responsiveness." They were considered to have more "nervous mannerisms" than the full-term children, for which oversolicitude on the part of the mother or other members of the family might be partly or wholly responsible. Shirley mentions primiparity, advanced age of the mother, and twinning as conditions more frequent in the families of premature children which, she believes, tend to predetermine for these children "a somewhat unusual environment that may foster the development of nervous habits."

In her discussion Shirley says:

"In their follow-up study of older premature babies Hess, Mohr, and Bartelme discovered an excess of nervous habits in prematures as compared to their term siblings. Apparently, therefore, nervous habits not only are engendered in infancy but also persist and are extremely difficult to break. This is particularly true of thumbsucking and of bladder incontinence. In consideration of the greater hazard in developing nervous behavior it would seem that mothers of prematures need a different type of mental hygiene from that given to mothers of term babies. Probably they should be discouraged from regarding and treating the baby as unusual or exceptional to any greater degree than necessary. They should realize that by allowing the baby to set his own developmental pace they are probably reducing to a minimum the hazard prematurity imposes on normal emotional development. They should be assured that his chances for making up his intellectual discrepancy are good, but they should not be given too much hope for eventual acceleration if he remains 'backward' beyond the age of 2."

Benton (13, p. 740) says of this study: "It is difficult to see how clear-cut conclusions can be drawn from the findings concerning the developmental status of the infants." He considers that the test norms were "uncertain" and the control group, being of higher economic status than the premature group, was inadequate. He regards the observations on "nervous mannerisms," however, as "impressive."

Shirley (91, pp. 117-127) also describes a group of personality traits that she believes to be characteristic of premature children. This tentative suggestion of such a "behavior syndrome" resulted from study of the records of 65 premature children (2 in addition to the 63 previously reported on) 6 to 30 months of age and of 30 premature children 2½ to 6 years of age, compared with those of a control group of "normal" children. The behavior syndrome has sensory and motor manifestations and emotional, social, and intellectual features, noted by the author and confirmed, she believes, by such data as are available in other studies. She suggests that "careful comparison of a group of prematures with a group of term children manifesting several features of the syndrome should reveal which aspects of the syndrome are attributable to prematurity per se and which are attributable to other factors usually associated with the care and training of prematures."

Other North American studies

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Two other studies have been made in the United States: Schwartz and Kohn (89) and Rosanoff and Inman-Kane (80). The former studied only 9 premature infants; the latter studied 146 premature infants of school age but according to Benton (13, p. 732) did not specify the intelligence tests used.

EUROPEAN STUDIES

Among European studies may be mentioned those of Brander (16), Asher (8), and Capper (23). Defects in material or methods may account for differences in results recorded in some of the studies on this subject. Though this discussion deals chiefly with studies of American children, the study by Capper made in Vienna, but published in this country, is analyzed because it has caused some unjustified pessimism with regard to the physical and mental development of premature infants. Capper says: "The fate of immature children is not enviable; almost one-half of them die during the first year of life. Of those that remain alive the majority are physically as well as mentally underdeveloped." His conclusion, however, is vitiated by the following weaknesses in his study:

- The children studied were from families of low socio-economic status and in addition, according to Benton (13, p. 728), were born at a period "when hospital facilities for the care of prematurely born children were very poor."
- 2. The control material was unsatisfactory.
- 3. Varied methods of testing were used, many of them not standard methods. For example, Capper (23, p. 459) states: "The older children were questioned about their grades in school . . . and the ones who were very much backward in school or who seemed mentally inferior were subjected to regular intelligence tests." Information about the ages at which sitting, standing, walking, and speaking began was obtained from the mothers.
- 4. Although Capper gives special consideration to birth trauma, there is no evidence that he excluded such cases in drawing his general conclusions with regard to the mental development of premature infants.

BENTON'S REVIEW OF METHODS AND CONCLU-SIONS

Benton (13, p. 722), in reviewing critically the studies that have been made on this subject since 1911, lists the conditions found in some of the studies that not only led to divergence but affected the reliability of the conclusions:

- "1. Until very recent times the method of estimating the intelligence of children has been that of 'clinical impression,' together with the utilization of such data as the child's school-grade status and parents' estimate of his intelligence. It is evident that so subjective and variable a criterion can hardly serve as a reliable measure of intellectual status. One investigator might consistently overrate the intelligence of a group of children being studied while another investigator might consistently underrate the intelligence of the same group of children.
- **"2.** Little attention has been paid to the socio-economic character of the group of children under investigation. The socioeconomic character of the groups studied . . . have varied widely, ranging from . . . children from middle-class homes whose fathers were, for the most part, in the professions to [those] in which the proportion of illegitimate children was 47 percent.

- **"3.** In some studies conclusions are drawn from the findings in an inadequate number of cases.
- "4. In other studies special selective factors bias the nature of the sample; e. g., that of [a physician] one of whose groups consisted of prematurely born children referred to him as a specialist in children's diseases. It is clear that a sample which includes only sick children cannot be considered adequate."

In the light of these considerations Benton summarizes as follows the results of his critical review of the studies on mental development of premature infants (**pp. 740-743**):

⁴⁷With two exceptions, all investigations dealing with [the developmental status of prematurely born children] show developmental retardation during the first 2 years of life. . . [The two exceptions are regarded by Benton as 'of questionable validity' on this point.]

"Gesell's careful studies indicate that the birth displacement does not significantly affect the rate of development of these children....

"While there is no agreement concerning [the intelligence of prematurely born children] in the literature in general, most of the more reliable studies indicate that, as a group, prematurely born children are not inferior to full-term children in respect to intellectual development. . . .

"The question [of a higher incidence of mental defect among premature children] is essentially an open one and deserves careful quantitative and qualitative investigation. . . .

"It seems reasonable to conclude that the factor of birth weight, within the range indicated (1,000-2,500 gm.), is not of great significance in relation to the mental development of children surviving the first year of life.

"A considerable number of investigators . . ., including authors of some of the more reliable studies and some authors who found that prematurely born children were not inferior to the average in respect to intelligence, have reported that the incidence of 'nervous traits' or behavior difficulties appears to be definitely higher among prematurely born than among full-term children. . . Despite the impressive list of authors who have reported these findings, the conclusion that prematures in general show a tendency to develop 'nervous traits' cannot be accepted as established fact, for a really well-defined and adequately controlled investigation of this question is lacking. . . . If a careful study of the incidence of behavior disturbances in the premature should confirm these reports of a generally higher incidence, a further study of the responsible factors would be called for."

(See also Psychologic Aspects of Care, p. 138.)

Summary

The prognosis for premature infants must take into consideration their chances both for survival in infancy and for normal growth and development, physical, mental, and emotional.

SURVIVAL

Statistics from selected hospitals that give good care and that have made special efforts to improve methods of care show that the chance of survival has improved in recent years. Though these figures are given for only four hospitals the conclusion seems justified that under good conditions of care the prognosis is as follows:

Weight group (gm.) Percent survival	Prognosis
2,001-2,500	At least 93	Excellent.
1,501-2,000	At least 82	Good.
1,000-1,500	At least 50	Fair.
Less than 1,000)	Very poor.

PHYSICAL GROWTH

In his longitudinal study based on repeated measurements of individual premature infants in the four birth-weight groups Ylppö found, with few exceptions, retardation in growth in weight and length in the first 2 to 5 years of life. At the conceptional ages 2 to 4 years the premature infants began to catch up to the norms, and most of them had done so at about the conceptional age of 5 to 6 years. The delay in growth was greater the smaller the weight and length at birth.

Retardation in growth of the thorax was found up to the conceptional age of 3 years. The growth of the head was least retarded.

Ylppö attributed the retardation in growth to immaturity itself and the associated factors of undernutrition and rickets, together with infections, endocrine dysfunction, and "inertness."

In their long-term study of the physical growth of North American premature infants Mohr and Bartelme found that growth is retarded, that there are sex differences in the rate of increase in weight, and that the interval required for premature infants to catch up to the norms is shorter than that reported by Ylppö. The premature boys in their series had attained the weight of their full-term brothers at 4 years and of the Woodbury norms at 3 years. The girls showed no reliable difference in weight from their siblings; they approximated the Woodbury norms at 9 to 12 months. Birth weight influenced the weight increase of both boys and girls, gain being more rapid in the higher birth-weight group. Within the age range studied (3 months to approximately 8 years) the children of lower birth weight did not tend to reach the mean weights noted for the larger prematurely born children and remained below the entire group and below the siblings and the Woodbury norms.

Only slight differences were noted in growth in length between the prematurely born boys and girls and their siblings and the Woodbury norms. The growth in length of the boys was somewhat more variable than that of the girls. The boys attained the length of their siblings and of the Woodbury norms at 3 years; the girls, at 18 to 24 months. Growth in stature, as in weight, was found to be less rapid among both boys and girls of lower birth weight.

Growth in head circumference also showed differences in relation to sex and birth weight. There was no evidence of persistent megacephalus among premature infants.

MENTAL AND EMOTIONAL DEVELOPMENT

Studies of mental and emotional development of North American premature infants have been made by Gesell and his coworkers, Mohr and Bartelme, and Shirley.

Gesell, on the basis of studies of individual infants over a period of years, concludes that when the age of the infant is reckoned from conception, prematurity per se does not markedly alter the normal course of mental growth.

Mohr and Bartelme found that comparisons of prematurely born children with full-term children (their siblings and a "standardization" group) "indicate that premature birth unassociated with intracranial injury does not affect mental development." They also found that prematurity per se and degree of prematurity (based on birth weight and period of gestation) are not related to mental development.

Shirley, on the other hand, reported that infants weighing less than 4 lb. at birth were retarded by a month or more throughout the period of 18 months that she covered, but that infants weighing 4 to 5 lb. at birth reached the norms at 9 months of age.

Mohr and Bartelme studied the "habit formation and social adaptation" of premature infants compared with full-term infants on the basis of information from the mothers and from psychometric tests. The premature infants were found to be slower than full-term infants in walking, in sphincter control, and in development of independent habits of feeding. Speech defects—especially stuttering—and temper displays were more common among the premature infants, and the oldest group were reported to be less self-reliant than the oldest fullterm group.

Shirley reported that developmental tests showed premature infants to be "more retarded in manipulative development than in intellectual grasp and social responsiveness." She suggests that the "nervous mannerisms" which she found to be prevalent among them might be related to the apprehensive state that the birth and rearing of a premature infant engender in the mother and to oversolicitude on the part of the mother or other members of the family.

Benton, who reviewed critically the studies that have been published on the mental and emotional development of premature infants, comments on the need for "well-defined and adequately controlled investigation" before the higher incidence of nervous traits or behavior difficulties in premature infants can be regarded as established.

Defects in material and methods of some of the studies on this subject are discussed. Benton lists some of these defects and summarizes the conclusions that may be considered validated by the available studies of the mental and emotional development of premature infants.

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PART II

Clinical Considerations

CLINICAL APPRAISAL

A clinical appraisal of the premature infant's general physical condition should be made at the time of birth, and this should be followed by a more thorough examination when the infant's condition permits.

When the birth of a premature infant is expected a physician, preferably a pediatrician, should be present at the delivery, with a nurse, to give undivided attention to the infant. There should be available equipment necessary for emergency care of the infant, such as proper equipment for keeping the infant warm, for clearing the respiratory tract, and for resuscitation if necessary.

It is important to appraise the individual infant's degree of prematurity and his general physical condition in order (1) to make a prognosis and (2) to outline the methods of care to be followed. This obviously requires considerable skill and experience and an adequate background of pediatric training, including knowledge of the normal full-term infant.

Immediate appraisal is largely a matter of observation and includes consideration of:

- 1. Adequacy of respiration.
- 2. Evidences of serious congenital abnormalities.
- 3. Appearance of the skin in relation to edema, jaundice, hemorrhage, or eruption.

Later appraisal includes:

- 1. Consideration of the mother's prenatal, labor, and delivery history.
- 2. Estimation of the degree of prematurity of the infant.
- 3. Detailed clinical examination of the infant.

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Estimation of the degree of prematurity cannot always be made, of course, on the basis of clinical findings, but the following points should be helpful:

An infant that is only 1 or 2 weeks premature will obviously appear not very different from a full-term infant. On the other hand, an infant that is born 3 weeks or more before term will differ markedly from the mature infant, and the more premature the infant, the greater the differences will be. It should be emphasized that the clinical evidences usually described are those of extreme prematurity and are therefore found in different degrees in infants of varying degrees of prematurity. (See fig. 12.)

The physician will take into account the birth weight, or, if this is not known, the present weight and the estimated gestation period.

Regardless of the estimated gestation period, if the infant weighs 2,500 gm. (5 lb. 8 oz.) or less he should be regarded as premature and, therefore, in need of special care. If he weighs at birth between 2,000 and 2,500 gm. the prognosis is usually good; if between 1,500 and 2,000 gm. it is usually fair; if between 1,000 and 1,500 gm. it is relatively poor; if less than 1,000 gm. it is very poor. There are a number of reports of the survival of infants weighing at birth less than 1,000 gm (2 lb. 3 oz.), but none of infants weighing less than 397 gm. (14 oz.) (235). For this reason the term "nonviable" should not be applied to any infant that at birth weighs about 400 gm. or more if evidences of life are present.

Handicaps of premature infants

Premature infants suffer from a number of anatomic and physiologic handicaps resulting from immaturity of the various systems that are not fully prepared to function until term.

- 1. The regulation of body temperature is handicapped by:
 - a. A surface area large in proportion to the weight, permitting excessive loss of heat by radiation.
 - b. A lack of insulating subcutaneous fat.
 - c. Feeble muscular development, with resulting low total heat production.
 - d. Incomplete development of the sweating mechanism.
- **2.** Respiration is handicapped by:
 - a. Incomplete development of capillaries of both the medulla and the lungs.
 - b. Incomplete development of the alveoli of the lungs.
 - c. Weakness of the muscles used in respiration.
 - d. Weakness of the thoracic cage.
 - e. Feebleness of cough and gag reflexes.
- 3. The nutritional processes are handicapped by:
 - a. Weakness of the sucking and swallowing reflexes.
 - b. Low acidity of gastric contents.
 - c. Small capacity of the stomach; tendency to distention and vomiting.

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- d. Incomplete storage of calcium and ascorbic acid.
- e. Poor absorption of fat.

- 4. The chances of infection are increased by:
 - a. Birth before transfer from the mother of protective antibodies.
 - b. Premature withdrawal of the placental barrier to infection.
 - c. Opening up of new portals of infection through skin, respiratory tract, and gastrointestinal tract.
- 5. The chances of injury to the central nervous system are increased by:
 - a. Fragility of capillaries.
 - b. Prolonged prothrombin time.
 - c. Premature subjection of delicate structures to forces of labor.
 - d. Tendency to breech presentation.
 - e. Frequent occurrence of anoxia.

In the following chapters the nature and clinical significance of these handicaps are discussed, in connection with the general care of the premature infant as well as the diagnosis and treatment of various conditions that are complicated because of prematurity of birth.

Physical examination

The physician, when he considers that the infant's general condition is such that there will be no hazard from a minimal amount of exposure and handling, should make a complete examination of the infant. The examination should be made as rapidly as possible and under such conditions that the infant will not be exposed any more than is absolutely necessary.

OBSERVATION

Before the physician makes any measurements or undertakes a complete physical examination, he should carefully observe the infant for evidence of cyanosis and other abnormalities. He should make sure that the infant's upper respiratory tract is clear and that respiration is well established. The examination should be made rapidly. The infant should be in a heated bassinet if possible. Otherwise he should lie in heated blankets or be kept under a heat lamp during the examination.

ACTIVITY

The less mature the infant the less activity there is. Activity is not always directly related to size, however, for some premature infants of low birth weight have good muscular activity and others of the same weight are completely inactive. Good muscle tone of the abdomen and extremities is a valuable prognostic sign.

GAG AND SWALLOWING REFLEXES

Gag and swallowing reflexes, which are usually very active in the newborn full-term infant, are often absent or feeble in premature



Figure 12.—Female infant, 14 days old, weighing 2 lb. Note that the skin of the extremities and neck is wrinkled; the chest is narrow and the ribs are prominent; labia minora very prominent; infant very active in spite of extreme prematurity (courtesy of Lewis K. Sweet, M. D., Gallinger Municipal Hospital, Washington, D. C.).

infants. Although the activity of these reflexes is no doubt related to the maturity of the infant, it is not always related to the infant's size. Some very small infants have active gag and swallowing reflexes. What constitutes the best method for administering the feedings of the premature infant depends on the activity of these reflexes. (See p. 171 for discussion of feeding methods.)

SKIN AND APPENDAGES

The skin is delicate, and because of the inadequacy of subcutaneous fat it may be loose and wrinkled. The nipples and areolae of the breasts are inconspicuous, the hair of the head is scanty, and eyebrows are usually absent. It is commonly stated that the nails of the fingers and toes do not usually reach the tips of the digits until about the ninth month of fetal age. Ylppö (408, p. 33) says, however: "According to a very prevalent but wrong belief, it is, for example, possible



Figure 12a.—Another view of Figure 12.

to judge the age of the fetus from the length and development of the nails. In fetuses from $6\frac{1}{2}$ to 7 months of age and with a birth weight of less than 1,000 gm. I have often seen nails reaching over the finger tips, though, according to the generally prevalent opinion, this could be the case only in an infant carried to term and of normal weight. Still less comprehensible to me is the belief, also very prevalent and wrong, that nails are completely lacking in the smaller premature infants. . . According to my experience it is possible to recognize the nails easily even in fetuses weighing 300 to 500 gm." (Notice the nails in fig. 12.)

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 that is only slightly premature may have a relatively small amount of subcutaneous fat.

BODY TEMPERATURE

The body temperature of premature infants tends to be low, and the more immature the infant the more difficult it is to stabilize the body temperature. Clinical observations suggest that one should not try to raise the premature infant's body temperature to "normal" for a mature infant but should rather supply moderate heat in order to maintain it at a constant level. If this is done and the infant is properly cared for he will tend to stabilize his temperature at a relatively low level, which will gradually become higher as he becomes more mature.

HEART AND CIRCULATION

After birth the premature infant's heart rate is relatively rapid, and the rate changes with changes in position and with activity. Sontag and Newbery (329) have studied fetal arrhythmia in utero and have found that they are common and are affected by external stimuli or chemical changes in the blood. Extra systoles occur and these authors consider that they are related to phases in the development of the automatic nervous system.

Murmurs may be present which eventually disappear; they are evidence of gradual anatomic closure of fetal openings which have actually ceased to function at birth.

Roentgenograms of the heart of premature infants are difficult to interpret because the thymus gland may obscure the upper part of the heart, and the incomplete lung expansion may make the heart borders difficult to see.

ABDOMEN

The abdomen is usually level or slightly depressed and soft. The wall is thin and the viscera are easily palpated. With slight distention the intestinal pattern may become visible. True distention is in itself a hindrance to respiration, since breathing is largely diaphragmatic.

The liver margin is usually palpable, as it is in the normal newborn infant. Palpation of the liver and other viscera should be gentle, as pressure, like distention, may impede respiration.

The tip of the spleen is usually palpable. It may be easily pushed up under the lower ribs.

The kidneys in fetal life are situated relatively lower than in the later neonatal period. Usually they are easily palpable in the premature infant, as they are in the full-term infant.

GENITAL TRACT

The more immature the infant the less well developed are the external genitalia. In the female the labia minora are relatively prominent. In the male the scrotum is small and the testicles are frequently undescended.

SUMMARY OF FAVORABLE PROGNOSTIC SIGNS

Birth weight more than 1,500 gm. (approximately 3 lb.). No cyanosis.

Some activity on stimulation.

Gag and swallowing reflexes active; i.e., takes feedings well.

Skin not wrinkled, some subcutaneous fat.

Body temperature stabilizes.

Absence of edema, jaundice, hemorrhage, or pathologic skin condition.

Symptoms of abnormal conditions

There are certain pathologic conditions to which premature infants are peculiarly subject in the neonatal period. These conditions may be associated with immaturity or maldevelopment of various organs and systems or with some disease process.

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Symptoms of such conditions are apnea, cyanosis, pallor, jaundice, hemorrhage, convulsions, edema, vomiting, diarrhea, fever, dehydration. These symptoms may occur singly or in combination.

To assist the physician, various pathologic conditions found in premature infants in the neonatal period and the symptoms associated with them are outlined below:

Apnea is a condition of suspended respiration. It is the result of any condition that interferes with the respiratory mechanism and with adequate oxygenation of the blood.

The commonest underlying conditions are those associated with birth:

- 1. Analgesics or anesthetics given to the mother during labor or delivery.
- 2. Birth trauma.

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- 3. Immaturity of the nervous system and the respiratory tract.
- 4. Maldevelopment of the brain.

Cyanosis is evidence of inadequate oxygenation of the blood, which may be due to any one of a variety of causes.

The commonest causes of cyanosis are:

- 1. Interference with the action of the respiratory center from an inadequate supply of oxygen or from increased intracranial pressure as a result of birth trauma.
- **2.** Obstruction in the respiratory tract.
- 3. Poor development of the accessory muscles of respiration.
- 4. Interference with lung expansion by:
 - a. Incomplete or abnormal development of the pulmonary system (lung tissue or bronchi).
 - b. Pressure on the lungs from an enlarged heart or from herniation of the abdominal viscera into the thorax.
- 5. Interference with diaphragmatic action by abdominal distention.
- 6. Cardiac malformations.
- 7. Poisons that produce methemoglobinemia.

Pallor is evidence of shock and hemorrhage. It is a rare symptom compared with cyanosis.

The commonest causes of pallor are:

- 1. Severe asphyxia in infants that fail to breathe at birth.
- 2. Severe intracranial injury with shock.
- 3. Anemia due to defective hematopoiesis, erythroblastosis, or hemorrhage, intracranial or visceral.

Jaundice may be physiologic, i. e., due to bilirubinemia in the early days after birth. This type of jaundice has no pathologic significance. If, however, the jaundice is present at birth or appears on the first day of life, if it is severe and persists, it probably is indication of:

- 1. Erythroblastosis.
- 2. Congenital bile tract anomaly or obstruction.
- 3. Septicemia.

Hemorrhage may be physiologic, traumatic, or idiopathic.

Bleeding from the vagina is usually physiologic, the result of activity of maternal hormones transmitted to the fetus in utero.

Causes of pathologic hemorrhage are:

1. Trauma during birth which may result in intracranial, visceral, subcutaneous, or submucous hemorrhages.

- 2. Hemorrhagic disease (hypoprothrombinemia), the cause of which is not known.
- 3. Septicemia.

Convulsions, which may be generalized or merely localized muscular twitching, may be symptoms of:

- 1. Intracranial birth injury.
- 2. Cerebral defect, congenital or the result of prolonged anoxia.
- 3. Hypocalcemia from:
 - a. Temporary hypoparathyroidism, or vitamin-D deficiency.
 - b. Alkalosis.
- 4. Hypoglycemia.
- 5. Effect of drugs used to stimulate respiration, particularly metrazole.
- 6. Kernicterus.

Edema occurs sporadically in premature infants in the early neonatal period. The cause is obscure. The condition is probably evidence of some metabolic disturbance associated with a relatively high water content of the body. Hypoproteinemia has not been proved to play a role in causing edema in the early neonatal period.

Vomiting in premature infants in the neonatal period may be due to a specific cause or may be merely a symptom of general illness.

The causes of vomiting are:

- 1. Congenital malformation of the esophagus.
- 2. Abdominal distention.
- 3. Administration of food too rapidly or in too large amounts.
- 4. Increased intracranial pressure.
- **5.** Pyloric stenosis.

Diarrhea in premature infants in the neonatal period may also be due to a specific cause or may be merely a symptom of general illness. The commonest causes of diarrhea are:

- 1. Low tolerance of alimentary tract, particularly to fat.
- 2. Infection, enteral or parenteral.

Dehydration. Premature infants tend to become dehydrated as a result of:

1. Unsuitable environmental conditions, i. e., high temperature and low relative humidity.

- 2. Impaired renal function.
- 3. Inadequate fluid intake.
- 4. Diarrhea or vomiting.

Fever. Elevations of temperature in premature infants in the neonatal period are difficult to interpret since the body temperature is readily affected by environmental conditions. Either dehydration or infection may be present with or without manifest fever.

Data in regard to causes and incidence of morbidity among premature infants in the neonatal period are meager compared with data on causes and incidence of mortality. The discussion of the various types of abnormal conditions (p. 182 ff.) deals with data available from the medical literature in regard to incidence, causes, diagnosis, treatment, and prevention, particularly as these conditions affect premature infants.

CARE IN THE NEONATAL PERIOD

General aspects of care

For the premature infant the neonatal period (the first 30 days of life) is fraught with more danger than any other period of life. Conditions surrounding birth and the first 24 hours after birth are especially hazardous, more than half the neonatal deaths of these infants occurring in this period.

There is general agreement among medical authorities that the chances for the premature infant's survival are greatly increased by expert hospital care. The methods of care discussed in the following pages are based on the assumption that the care will be given in a hospital.

Some premature infants will, however, be born at home, either because home delivery is planned or because premature delivery, after a short labor, occurs precipitously. The physician must make the decision whether the infant should be transported to a hospital or receive care at home. The general principles of home care are similar to those of hospital care but certain modifications and adaptations are necessary under home conditions. Reference to some of these will be made in the sections that follow.

Methods of care in the early period necessarily differ from those after some adjustments to extrauterine life have been made. Consequently the detailed discussion of care will be taken up in three parts: (1) care at the time of birth; (2) care in the first 24 hours after birth; and (3) care in the later neonatal period. The general principles of care in these three periods will be presented first in outline form followed by more detailed discussion of certain methods of care applicable to all three of these periods.

CARE AT BIRTH

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At the time of the birth of a premature infant, experienced medical and nursing care, as well as suitable equipment, is essential to saving the infant's life. There should be an experienced physician and nurse in the delivery room whose sole responsibility is to give emergency care to the infant.

- 1. The delivery room should be warm, $70^{\circ}-75^{\circ}$ F., and everything should be in readiness for the birth of a premature infant since any delay may be fatal.
- 2. In order to conserve the infant's body heat, a sterile blanket that has been warmed should be ready for the reception of the infant on the delivery table. A heat lamp may be used to keep the infant warm prior to clamping the cord.
- 3. To clear the infant's respiratory tract of mucus and fluid, a soft rubber suction bulb or a catheter with mucus trap in

a sterile package should be at hand. To aid in maintaining or establishing respiration a supply of oxygen and equipment suitable for administering it should be available in the delivery room. (For methods of resuscitation and oxygen therapy see pp. 117-119.)

- 4. Provided the infant does not need emergency treatment for anoxia, the cord should not be clamped until pulsation has ceased if the infant is to receive the full complement of placental blood.
- 5. The infant should be removed from the delivery table to the incubator or bassinet which has been warmed for his reception when the physician conducting the delivery has completed his part of the infant's care. (See p. 124 for incubator care.)
- 6. The physician should then make an appraisal of the infant's general condition to determine:
 - a. The adequacy of respiration. (See p. 116 ff for methods of clearing the respiratory tract and initiating and main-taining respiration.)
 - b. Any evidences of serious congenital abnormalities.
 - c. The appearance of the skin in relation to jaundice, hemorrhage, or eruption.
- 7. Identification of the infant should be made at birth. (See p. 132.)
- 8. Eye prophylaxis should be attended to in the delivery room. (See p. 248.)
- 9. Present information seems to indicate that vitamin K should be given to the infant regardless of whether or not the mother has received vitamin K during labor. (See p. 166.)
- 10. The infant should not be moved from the delivery room until the physician indicates that the infant's condition permits transportation. A heated bed or a carrier should be used. (For carriers see p. 128.) The nurse should accompany the infant during transportation.

CARE IN THE FIRST 24 HOURS

During this period as well as throughout the neonatal period the environmental conditions in the nursery should be optimal for the infant. (See **360**.) The conditions are described on page 121.

A physician should follow the infant's course in the nursery with the same interest and care that he does in the delivery room. If immediate treatment is needed the physician should remain with the infant until such treatment is given and until the effects of the treatment are satisfactory. The physician should leave written orders for the general care and treatment of the infant and he should be on emergency call during this critical period.

A nurse experienced in the care of premature infants should be in constant attendance to assist the physician, to carry out certain treatments, and to observe the infant for any abnormal symptoms, such as cyanosis, vomiting, convulsions, and hemorrhage. (For discussion of significance of these symptoms see p. 108.) The nurse should be given instructions in regard to her procedure in case the infant has any of these symptoms. A complete understanding between physician and nurse as to procedures in case of emergency is also essential.

Facilities for care and treatment of the premature infant which are especially adapted to them should be in constant readiness. They include some type of suction and resuscitating apparatus with a supply of oxygen; a source of blood for transfusion and suitable apparatus for administering it; and suitable solutions ready for subcutaneous and intravenous administration.

CARE IN THE LATER NEONATAL PERIOD

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Conditions favorable to the infant's welfare during this period are similar to those in the first 24 hours after birth: briefly, skilled medical and nursing care; optimum environmental conditions; suitable equipment for diagnosis and treatment of abnormal conditions. In addition, each infant must receive a careful physical examination; must be protected against infection; must be fed according to his special needs; and must receive suitable care of the skin and be supplied with suitable clothing. Records, both medical and nursing, must be kept in such form that they are useful for immediate care, for giving a prognosis, and for determining when the infant is ready for hospital discharge. Before date of discharge, the home must be appraised and deficiencies supplied. This may entail working out a plan of cooperation with health and welfare agencies in the community.

CRITERIA FOR DISCHARGE FROM HOSPITAL CARE

The time at which a premature infant may safely be discharged from the hospital is not necessarily related to any one factor such as weight or age.

In many hospitals the attainment of a weight of 2,500 gm. (5 lb. 8 oz.) is arbitrarily set as the criterion for discharge from the hospital, provided the infant is well and the home conditions are adequate for his reception. Many premature infants may be safely discharged before they attain a weight that indicates maturity and there are certain advantages in release from hospital care as soon as it is deemed safe for the infant. Important reasons for discharge from the hospital as soon as possible are:

- 1. The establishment of normal mother-infant relationships from the point of view of breast feeding and normal emotional responses of mother and infant (see p. 138).
- 2. Avoidance of infection, the chances of which are increased by prolonged nursery stay.

In making the decision as to time of discharge, the individual infant's condition, the intelligence and cooperation of the mother, and the home conditions should all be given careful consideration.

Before the mother leaves the hospital she should be instructed in regard to the care of her infant, including maintenance of her breastmilk supply. At least a week before the expected date of discharge, arrangements should be made with nursing and social agencies serving the community in which the home is located to appraise the home as to its suitability in regard to such matters as:

Whether the other persons living in the home are well.

Whether the mother will be able to care for the infant herself. Whether the housing arrangements are suitable for care of the infant.

Whether the parents are financially able to provide proper food, clothing, and other essentials for the infant.

If the home situation is unsuitable for the infant, arrangements should be made with a family-service or other agency to assist in preparing the home for the infant and in making necessary adjustments.

If, after discharge from the hospital, the infant is not to continue under the care of the physician who cared for him in the hospital, the family physician or a community agency should be notified that the infant is to be discharged, so as to insure continuous medical supervision for the infant, including supervision of diet and hygiene, and medical care.

For mothers who need such services, arrangements should be made with a public-health nursing agency for early and continued instruction at home.

Respiration and oxygen therapy

Schmidt (311, p. 469) describes the respiration process as follows: "Respiration in an air-breathing animal . . . involves the coordinated participation of tissue fluids, blood, the circulation, many muscles, and a considerable part of the central nervous system. For the sake of convenience, the factors concerned may be grouped as follows: (1) the gas exchange between tissue cells and the fluid medium surrounding them, which is called *internal respiration*; (2) the transport of gases between the tissues and the lungs by means of the blood; (3) the exchange of gases between the blood and the air in the lungs, which is *external respiration*; (4) the mechanics of external respiration including its regulation through the central nervous system. These factors must be considered separately, but it should be borne in mind that they are all parts of one process having only one fundamental purpose, which is to supply the body cells with the oxygen they require and to remove the carbon dioxide they produce."

When an infant is prematurely born, the first problem that presents itself is the initiation of respiration. The proportion of infants who breathe spontaneously at birth is much less among those born prematurely than among those born at term.

CAUSES OF DELAYED RESPIRATION

The causes of delayed respiration in premature infants are numerous and are related both directly and indirectly to prematurity. The commonest of these causes are:

- 1. Action of respiratory center in the brain inhibited by:
 - a. Traumatic intracranial hemorrhage.
 - b. Analgesics and anesthetics administered to the mother during labor and delivery.
 - c. High threshold of the respiratory center to chemical and other afferent stimuli probably associated with immaturity of cells, inadequate vascularity, and possibly de-

ficient carbonic anhydrase and underdevelopment or unresponsiveness of the carotid and aortic bodies.

- 2. Reduced oxygen supply to the blood resulting in asphyxia due to:
 - a. Mechanical pressure on cord.
 - b. Premature separation of the placenta.
 - c. Maternal anoxia.
 - d. Tetanic contractions of the uterus when oxytocic drugs are used.
- 3. Abnormalities of the lungs such as:
 - a. Immaturity of lung tissue interfering with gaseous exchange.
 - b. Congenital abnormalities.
 - c. Pneumonia.
- 4. Obstruction of bronchi and/or alveoli due to aspiration of fluids or mucus.
- 5. Mechanical compression of lungs by abnormal conditions within the thorax (pneumothorax, cardiac hypertrophy) or in the abdominal cavity (distention interfering with diaphragmatic action) and herniation of abdominal viscera into the thorax.

MECHANISM OF ONSET OF EXTRAUTERINE RESPIRATION

By his studies on fetal sheep, Barcroft (29) has contributed to the knowledge of the mechanisms involved in the onset of extrauterine respiration. He found that the "machinery of respiratory movement" started as part of a general reflex movement of the body in which the diaphragm took part. Movements later became rhythmic and still later the respiratory movement became more and more detached from somatic movement. When this whole mechanism became perfected, it came under the influence of central-nervous-system inhibition but could always be evoked by sensory stimulation. ". . . whether the foetus shows respiratory movements or not depends on the balance between inhibition and sensation."

At birth inhibition is depressed by asphyxia and respiratory efforts ensue. In addition, the brain "emerges from a sensory vacuum and is bombarded with volleys of sensation, which raise the general sensitivity." For sensation to have its full effect, the brain must be well oxygenated. The processes of labor and certain anesthetics given to the mother during labor and delivery, and interruption of the cord circulation reduce the oxygen supply to the fetus. Barcroft describes the "urge to breathe" as follows: When the umbilical cord is occluded the oxygen supply is cut off and CO₂ accumulates. He poses the question as to whether excessive CO₂ has a stimulating effect on respiration. After weighing the evidence from his own experiments, as well as those of Snyder and Rosenfeld; Eastman, Geiling, and DeLawder; and Windle, Barcroft concludes: "There seems to be no doubt that CO₂ will induce, or at all events accentuate, respiratory movements under suitable circumstances." Augmented respiratory movements have also been observed in the sheep and the cat from administration of oxygen mixed with CO₂ (8 and 10 percent respectively). Sensory stimuli of various types also play a role in initiating respiration,

among them rise of blood pressure from occlusion of the cord and stimuli from the skin, muscles, and joints.

In regard to methods of initiating respiratory movements in the human fetus at birth when they do not occur spontaneously, Barcroft (29) says that sensory stimuli should be initiated in the presence of a rich atmosphere of oxygen. He concludes by pointing out that the mechanism of onset of respiration is not by any means fully understood. Eastman (94, 95) has presented evidence that in asphyxiated infants, the tension of carbon dioxide in the blood is "usually almost twice that found in normal babies." He and his associates (95) were "unable to establish any optimal range of carbon-dioxide tension particularly favorable for the onset of respiration." Eastman considers on the basis of his studies that the asphyxiated human infant at birth suffers from anoxia (oxygen want) and that oxygen and not CO_2 should be given.

Noguchi (251) found a marked lowering of the pH of the fetal blood and concluded that asphyxia neonatorum is a state of uncompensated alkali deficit in consequence of oxygen want.

Recently it has been found that there are other factors that play a role in the asphyxiation of premature infants. An enzyme, carbonic anhydrase, favors the release of carbon dioxide and thus makes oxygen more readily available to the blood. Schmidt (311) points out that there are reflexes from the aorta and carotids which play a role in respiratory mechanisms. The respiratory reflexes arise in specialized receptors in the arch of the aorta and in the region of the carotid sinuses and are carried by the same nerves as the circulatory reflexes. He concludes, however, that "although the existence of the reflexes has been clearly proved their significance in the control of breathing is still uncertain."

The premature infant's respiratory mechanism may be handicapped because his blood is more deficient in carbonic anhydrase than the fullterm infant's blood and the aortic and carotid bodies become inactive in the presence of anoxia. The relation of carbonic-anhydrase deficiency in premature infants to cyanosis and respiration difficulties is not fully understood, and more research is needed. (For further discussion of the physiology of respiration, see **399**.)

METHODS OF STIMULATION OF RESPIRATION

The practical aspects of the problem must now be considered: How can we initiate respiration in a premature infant that fails to breathe? How can we increase the adequacy of respiration in one that has breathed and then stops breathing or breathes inadequately?

A great variety of methods for stimulating respiration in newborn infants can be found in textbooks and in current medical literature, but there is still much to be learned. Actually we know better what not to do than what to do.

Whatever is done to stimulate respiration must be done quickly and in such a way as not to injure the infant.

There are certain precautions that should be taken at the birth of a premature infant whether asphyxiated or not:

1. A physician and a nurse should be present whose only responsibility is to attend the infant and who have had experience in resuscitating infants and are familiar with the various methods.

- 2. Everything needed for resuscitation should be in readiness before the birth.
- 3. From the moment of birth the infant should be kept warm.

GENERAL MEASURES FOR RESUSCITATION

Immediate measures to stimulate respiration must be carried out on the delivery table. When prolonged stimulation is required, the infant, after the cord has been cut, should be placed in a heated bassinet or incubator or in a suitable resuscitator under the care of a nurse and a physician, both expert in methods of resuscitation of infants.

The following equipment essential for the resuscitation of the premature infant should be in readiness in the delivery room:

- 1. Soft rubber suction bulb, or small catheter with suction bulb and mucus trap when suction is applied by mouth.
- 2. A suitable type of mechanical resuscitator.
- **3.** A supply of oxygen and suitable equipment for administering it to premature infants.
- 4. A hypodermic set and stimulants (caffeine sodium benzoate and epinephrine).

If spontaneous respiration does not occur, appropriate and safe methods to induce respiration should be used. The infant should, first of all, be placed in a warm sterile blanket. The head should be kept level with the body and turned to the side to facilitate drainage from the mouth. Lowering of the infant's head below the level of the body, although often advocated, is dangerous if the infant is suffering from an intracranial injury. Then the procedure is as follows: The upper respiratory tract should be cleared gently. Mucus and other fluid that drains from the mouth should be wiped away with soft sterile gauze. The upper pharynx should be gently sucked out with a soft rubber suction bulb or with a small catheter attached to a suction bulb, with a mucus trap if mouth suction is used. A mechanical suction apparatus may be used but in using mechanical means the force of suction should be automatically limited. If, after the upper respiratory tract is cleared, the infant fails to breathe, respiration must be induced mechanically at the same time that oxygen is given. (For methods of administration of oxygen, see p. 120.) Delay in the onset of respiration may be fatal or result in damage to the central nervous system. Before discussing these mechanical methods of resuscitation, it should be pointed out that in an emergency, mouth-to-mouth insufflation may be used. There should be a protective layer of gauze placed over the operator's mouth.

It should also be pointed out that if the infant has not breathed there is no use and great danger in attempting manual "artificial respiration," i. e., rhythmic hand pressure on the chest or flexion of the knees on the chest. No amount of external pressure can cause any pressure changes in the thorax when the lungs are completely unaerated. In cases in which some aeration of the lungs has occurred some pressure changes may be accomplished, but the thoracic cage is so small and the supporting tissues so soft that more damage than good will probably result from manipulation. Even in full-term infants rupture of the liver may be caused by forcible attempts at resuscitation. Hanging by the feet and spanking, and "dunking" in hot and cold water are treatments that should never be used with premature infants. The former procedure increases intracranial pressure; the latter may produce shock.

It is dangerous to give such drugs as alphalobeline, coramine, or metrazol to stimulate respiration. Caffeine sodium benzoate, gr. $\frac{1}{4}$ to $\frac{1}{2}$, or epinephrine, 1-2 minims of 1-1,000 solution, may be used as stimulants.

TYPES OF MECHANICAL RESUSCITATORS

A "resuscitator" or a "respirator" is a device so constructed that controlled positive and negative intrathoracic pressure may be rhythmically produced while an oxygen-air mixture is being administered through the pharynx. Obviously the use of any one of these mechanisms must be preceded by the *clearance of the respiratory tract* and the provision of a favorable warm environment for the premature infant.

There are several types of apparatus available. Among the earlier types was a modification of the Drinker respirator but this type of respirator has been found unsatisfactory for infants. Several newer types of resuscitators are available. It is difficult to evaluate their safety and efficiency, for data on results of their use are not available. It is preferable to use a type of resuscitator that is so constructed that the rhythm and shut-off are controlled by the operator's hand.

Most of these machines consist simply of a gas tank provided with regulators for mixing oxygen and air, and for controlling the pressure and rate of flow. A face mask is provided with an intake and outlet valve, the former to deliver the gas to the posterior pharynx and the latter to allow for escape of expired air during the deflation period. Some machines have beds attached which are electrically heated; some have suction apparatus attached also.

Kreiselman (187) recommends that pressure be regulated so that the maximum is 16 mm. of mercury (average pressure used is 12 mm.); the rate of flow, 4 meters per minute; and the rhythm about 12 to 15 inflations per minute. He points out that "the head should be extended and the chin held up in order to maintain a clear airway."

There are certain objections to the use of any type of positive pressure machine, particularly for premature infants:

- 1. The exact intrapulmonary pressure that is safe to use has not been determined. Too high pressures may rupture the alveoli and, by producing pneumothorax, handicap the respiratory process.
- 2. If the glottis is closed, the air will enter the gastrointestinal tract and may thereby interfere with diaphragmatic action.
- 3. Mechanical rhythmic pressures may interfere with spontaneous respiratory rhythms that may be initiated.

In discussing resuscitators and inhalators it has been pointed out by the Council on Physical Therapy of the American Medical Association (19) that "the process of blowing oxygen into the lungs and aspirating it has a reverse effect on the circulation from that of normal respiration. Normal respiration tends to facilitate the exchange of gases in the lung capillaries. When the lung is inflated, even at very moderate pressures, circulation through the lung capillaries is retarded for an instant, since the blood pressure in these capillaries is very small. Stoppage here necessarily affects the entire circulation. However, periodic stops last only a moment, since the peak pressure (14 mm. of mercury) is maintained for only a short part of the cycle." Wilson (398) also states: "Any partially functioning respiratory system opposes by a reflex expiratory effort air blown into the larnyx and trachea and probably has an opposite action when suction is applied. The pulmotor type machine by its positive pressure prevents the normal effect of respiration on pulmonary circulation and probably, to some extent, inhibits this circulation."

Tracheal catheterization and insufflation has been advocated by Flagg (103, pp. 78-81). "The principles are exposure of the field (laryngoscopy under direct vision), removal of foreign matter (suction of fluid and relief of obstruction) and treatment directly to the damaged area with precision, dispatch, and absence of trauma (intubation by direct vision and insufflation of oxygen and carbon dioxide under controlled pressure)." In the hands of skilled operators trained by Flagg the method may be effective but no case reports of the use of this method in resuscitating premature infants have been found.

Crosse (70, p. 77) advocates the use of the rocking method to resuscitate premature infants. She advocates holding the infant in the arms wrapped in a blanket and alternately raising and lowering the body of the infant in a longitudinal direction at the rate of 10 times per minute. This is a modification of a new method for resuscitation of drowned persons reported by Eve (99). This method will be ineffective in an infant that has never breathed.

Millen and Davies (232) have described an apparatus to rock an infant mechanically with a view to combating asphyxia. This consists of an open-top lucite box so arranged on the platform of a compartment containing an electric motor, that one end of the bassinet can be raised and lowered rhythmically at a given rate per minute. It is advisable to withdraw as much mucus as possible with the first lowering of the baby's head because elevating the head tends naturally to make the baby aspirate the mucus. It is possible in this apparatus to supply oxygen by flooding it into the lucite box.

No detailed data are supplied by Crosse or by Millen and Davies on the results of the use of this method.

INDICATIONS FOR USE OF OXYGEN

For infants that have respiratory difficulties at any time in the neonatal period oxygen administration is always indicated. Oxygen is of great value particularly in the treatment of premature infants. It should be used freely but care should be taken to give it in proper dosage and by methods that are suitable for these small infants.

The chief indications for the use of oxygen are: respiratory difficulties, cyanosis from any cause, and a general feeble condition. Some authorities advocate giving oxygen to all very small premature infants.



DOSAGE OF OXYGEN

Room air contains 20.93 percent oxygen. (Room air at sea level, when freed of water vapor contains 20.93 percent O_2 by volume, 0.03 percent CO_2 and a residue designated as nitrogen, of 79.04 percent. See **311**, **p. 483**.) For premature infants "a 38-42 percent oxygen-air mixture answers most indications for increased oxygen," according to Hess, Mohr, and Bartelme (149, **p. 415**). Higher concentrations

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may be necessary for purposes of resuscitation, these authors state. Eighty percent oxygen appears to be the maximum concentration that they use.

POSSIBLE DANGERS OF OXYGEN THERAPY

Concerning the danger of oxygen overdosage Schmidt (311, p. 603) says: "This depends on the observation made by several investigators that animals that have been caused to live in more than one atmosphere of the pure gas for some time develop symptoms of pulmonary irritation, which may lead to pneumonia. By the best methods of administration, however, a concentration of not more than 85 percent of oxygen can be attained in the alveoli. Karsner has shown that under such conditions there is no danger in inhaling pure oxygen, even for long periods of time."

Stadie, Riggs, and Haugaard (334, p. 99) in reviewing the litera-ture on oxygen poisoning state that: "Any discussion of oxygen poisoning naturally requires consideration of the maximum non-deleterious dose of oxygen at various pressures above the normal of 0.2 atmos-The conservative conclusion by the majority of those experiphere. enced in oxygen therapy is that 0.6 atmosphere of oxygen is relatively safe for an indefinite period and 1 atmosphere for about 24 hours. . . Young animals appear to be relatively resistant to the toxic action of high pressures of oxygen." Stadie and his coworkers report that this increased tolerance has also been observed by Chapple in the human young. Employing a special incubator which permitted treatment without intermittance at oxygen pressures never less than 0.85 atmosphere, Chapple treated premature infants weighing less than 3 lb., for periods frequently as long as 3 weeks. During treatment the hu-Under these circummidity was maintained close to 100 percent. stances, he observed no poisonous action of oxygen whatever.

Stadie and his coworkers also point out that part of the deleterious action of oxygen, especially upon the lungs, may be due to its dryness when administered. They report that no papers discussing the relation of oxygen poisoning to the degree of humidity were found.

METHODS FOR ADMINISTRATION OF OXYGEN

Oxygen sold especially for medical use is available in various standard-size tanks. (Oxygen sold for commercial use is used in many hospitals for therapeutic purposes and is satisfactory for treatment of premature infants. It is usually available only in the larger tanks.) A small-sized tank is available for portable sets. The steel cylinder of the tank is filled with gas which is compressed to a pressure varying from 1,500 to 2,000 pounds per square inch.

For administering the gas the following apparatus is essential:

- 1. A regulator to control the oxygen flow and pressure.
- 2. Two gauges, one to show the pressure within the tank and the other the rate of flow of gas to the infant.
- **3.** A flask containing water through which the gas is bubbled to moisten it before it reaches the infant's respiratory tract. Gas delivered in a dry state has an irritating effect.
- 4. If the gas is delivered directly to the infant's respiratory tract there should be a gas bag equipped with a pressure blow-off device.

There are several methods used for giving oxygen to premature infants but some of these are unsatisfactory. Delivery of oxygen through a funnel placed over the infant's nose and mouth may be used for temporary emergency treatment, but this method is impractical for administering oxygen to these small infants over long periods of time.

Diffusion of oxygen into an open top or closed incubator or crib is an effective method for prolonged oxygen therapy.

- "Open box" method: The infant is placed in a bassinet or incubator, closed except for the top, and the oxygen is fed through a tube fastened to the mattress near the infant's nose. For premature infants, according to Burgess, Briggs, and Burgess (54) the oxygen flow should be regulated at the rate of 1½ liters per minute to give the required oxygen percentage. The carbon dioxide diffuses up and out and no ice is needed because of free circulation.
- 2. Closed method (oxygen tents or chambers): With the closed method of oxygen administration the tent or incubator should be so constructed that the infant can be easily seen. In non-air-conditioned incubators provision for cooling should be made if oxygen is used for a long period.

There are types of oxygen hoods that can be placed over the tops of bassinets which are designed for continuous use and are made of fireproof pliofilm. A completely enclosed air-conditioned incubator makes a satisfactory oxygen chamber provided it is so constructed that there is no fire risk. (For specifications for incubators see p. 371.)

Other techniques for administering oxygen are advocated. The use of resuscitators is discussed on page 118, and the intratracheal insufflation of oxygen on page 119.

Subcutaneous administration of oxygen has been advocated and is used in Sweden for treatment of premature infants. (Personal communication from the clinic of Dr. Kurt Gillingsvaard, Stockholm). No reports of treatment of premature infants by this method in this country have been found. According to Flagg (103) numerous observers have reported the relief of anoxemia by subcutaneous injection of oxygen, but since oxygen absorption is slow when administered in this way other factors must be responsible for the effect, possibly reflex stimulation of respiration from stimulation of the skin.

In addition to these measures, clinical experience has shown that repeated small transfusions of matched and typed whole blood have a stimulating effect on the respiration of the premature infant. This may be the result of supplementing the deficient carbonic anhydrase in the blood of the infant.

Environmental conditions

TEMPERATURE AND HUMIDITY

Within the uterus the fetus lives and grows in a favorable environment. The body temperature is automatically controlled by the metabolic relationships between the fetus and the mother and by the protection of the amniotic fluid within the uterine walls. During the last weeks of pregnancy the sweat glands are developed and the in-

sulating layer of subcutaneous fat is laid down, developments which help to prepare the infant for the rigors of extrauterine existence.

But when the infant is born prematurely, he has not yet developed these safeguards for extrauterine life. His layer of subcutaneous fat is poorly developed; his sweating mechanism is incomplete; and his surface area is great in proportion to his weight. His total catabolism is low because of his relative inactivity and because he is unable in the early period after birth, to take enough food to provide adequate calories for heat production.

The mechanisms that are involved in the inadequate regulation of body temperature in premature infants have been studied by Day and his coworkers (79). Preliminary to the studies a special calorimeter was designed by and constructed under the supervision of Day and Hardy (80) in order to study heat production and heat loss in premature infants. Using this calorimeter, Day, Curtis, and Kelly (79) made observations on 25 healthy male premature infants weighing less than 2,500 gm. at birth. The range in weight at the time of observation was 1,440-2,900 gm. A few infants were observed during the first week of life; the majority were in the second or third week.

Day makes the following statement with regard to his observations on premature infants (personal communication from Richard Day, M.D., Babies Hospital, New York City, June 1948):

"Premature infants have an unstable body temperature. In order to maintain a uniform body temperature, the environment must be regulated with more care than is the case for full-term infants. Under hot conditions premature infants get an elevation of body temperature above normal which is often considerable. The reason for this hyperthermia is a deficiency in the amount of sweat which is secreted. Peripheral vasodilation takes place normally, but as in the case of individuals suffering from ectodermal defect, with absence of sweat glands, vasodilation alone is not enough to prevent hyperthermia even under conditions mild enough to be considered tolerable by normal adults. Hypothermia likewise occurs frequently, but here again, the defect does not seem to lie in the insufficiency of vasoconstriction. It is caused rather by a very large surface area in proportion to weight, by thin subcutaneous tissues, and above all by a low metabolic rate and diminished muscular activity.

"Gordon and his coworkers found that under average conditions of activity throughout the 24 hours the total metabolism of premature infants was only 18 percent above the basal level, while full-term infants could elevate the rate of heat production by 40 percent under similar conditions. Of course, in a sick infant or in one still suffering from the shock of delivery, a vascular defect may be present, but such infants have not been studied with care in this respect."

Day, Curtis, and Kelly point out: "It is worthy of comment that most of the rectal temperatures [of the premature infants] in this study were below 37° C. (98.6° F.)." Perhaps the normal rectal temperature is actually lower in premature infants than in full-term infants. From the data these authors obtained they concluded that "healthy premature infants do not suffer, as a group, from a defect in circulatory adjustments to different air temperatures. They do have an inadequate production of sweat, a large surface area, and a poor layer of insulating subcutaneous fat for protection against heat loss."

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The optimum environmental conditions as far as they are known can be met in a number of ways, by air-conditioning the nursery, by providing air-conditioned incubators, or by using incubators that are not air-conditioned but in which the temperature is automatically controlled and which also have provision for increasing the humidity.

AIR-CONDITIONED NURSERIES

Yaglou, Drinker, and Blackfan (405) first described apparatus for air-conditioning nurseries for premature infants in hospitals. Later Blackfan and Yaglou (37) reported the results of a study of the effects of different atmospheric conditions on the growth and development of premature infants. This study, although reported as long ago as 1933, gives us the only standards for the environmental requirements of premature infants.

The authors' conclusions (p. 1195) are as follows: "Summarizing the results of a four-year study of the influence of air conditions on body temperature, it was found that the relative humidity best suited to the needs of premature infants is about 65 percent. With this humidity, the temperature requirements ranged from 75° to 100° F., depending on the general condition of the infant and the body weight. A humidity of about 30 percent or less tended to promote instability of body temperature and produced other untoward effects and fatalities."

In many instances the authors based their percentages on small numbers of cases. Apparently they did not determine the statistical significance of these differences. The figures appeared, however, to be consistently in favor of the beneficial effects of air-conditioning on premature infants, when temperature-humidity relationships were held within certain limits.

Blackfan and Yaglou also pointed out (p. 1193): "In connection with the recommendation of 65 percent relative humidity, it is important to emphasize that in nurseries heated by radiators and ventilated by natural means, the problem of controlling the humidity is difficult, particularly in cold weather. Not infrequently the relative humidity is lowered to 15 percent or less as a direct result of artificial heating. A large quantity of water must be evaporated to raise the relative humidity to 65 percent and this can be accomplished satisfactorily only by the use of mechanical humidifiers, the reason being that the actual moisture content of cold outdoor air is very low compared with what is required indoors. For example, if a room 12 by 15 by 10 feet is to be kept at 77° F. and at a relative humidity of 65 percent when the outdoor temperature is 20° F. and the outdoor relative humidity 65 percent, it would be necessary to evaporate a minimum of 3 pounds of water per hour in order to maintain the desired humidity. This is with natural ventilation through windows and doors to the extent of about two changes of air per hour. With 25 changes of air per hour, as in this investigation, 371/2 pounds, or 4½ gallons, of water must be evaporated per hour to produce the optimum result. From these figures it is easy to see that evaporation from a pan of water on the radiator or from a wet sheet would be entirely inadequate."

Yaglou reports that for air-conditioning nurseries "the best system is a spray-type year-round air-conditioning unit capable of maintaining your nursery at 75° F., $\pm 1\frac{1}{2}$ ° F., with 60 percent relative

humidity and with not over 50 percent circulation in the warmest summer weather. It should provide for a maximum of 10 air changes per hour in winter, all from outside, with an air movement, all from outside, of not over 35 feet per minute at the level of the cribs. It is best to install the apparatus in the basement or in an adjoining room." (Personal communication from C. P. Yaglou, M. D., to E. A. Park, M. D., January 1945.)

If central air conditioning cannot be obtained, portable room coolers should be used during hot weather. In the winter when the nursery is artificially heated some device for increasing and automatically controlling humidity is needed. It is not possible appreciably to alter the humidity with such devices as pans of water on radiators, hanging wet sheets, or so-called "humidifiers." It is possible to control the humidity by attaching to the steam valve of steam radiators an apparatus to control automatically the amount of steam allowed to escape into the room.

If air-conditioned nurseries are not available suitable temperaturehumidity relationships can best be maintained by the use of incubators. For the smaller infants, even in air-conditioned rooms, incubators may be necessary to maintain the body temperature.

INCUBATORS

Hess (147) has studied the history of incubators and finds that they have been used to maintain the body temperature of premature infants for more than a hundred years.

The clinician who contemplates the purchase of an incubator wishes to obtain one which will maintain the body temperature of the premature infant at the point that he considers "optimum"; which will regulate the relative humidity of the air within the incubator; which will not be a fire hazard, particularly when oxygen is being used; and which will provide for ventilation. (See specifications, appendix 4, p. 371.)

For the clinician faced with the problem of selecting an electrically heated incubator, the only guides available are the information furnished by the manufacturers, the experience of physicians and nurses who have used the incubators, and the specifications drawn up by the Children's Bureau and the National Bureau of Standards (90).

Many types of incubators are now available which vary greatly in price, construction, and method of operation.

Types of incubators

Incubators may be grouped into two main types:

- 1. Completely enclosed incubators.
 - a. Air-conditioned so that temperature, humidity, and air circulation are automatically controlled. (See 53, p. 2, and fig. 13.)
 - b. Not air-conditioned. (a) Those in which temperature and humidity are automatically controlled but circulation of air is not automatic (fig. 14), and (b) those in which only the temperature is automatically controlled.
- 2. Partially enclosed incubators. (a) Hood-type incubators that fit over the bassinet and cover the body and extremities but not the head of the infant (fig. 15); (b) open-top incu-

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Figure 13.—One kind of completely air-conditioned incubator.



Figure 14.—One kind of incubator with automatically controlled temperature and humidity (Washington Post Photo).



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Figure 16.—Simple box-type incubator heated by hot-water bottles.

bators of the water-bath type, or heated bassinets with the heat units under the bassinet (fig. 16).

Functions of the incubator

Incubators have the following functions:

- 1. To maintain the environmental temperature, and preferably also the relative humidity, constantly at a point that will prevent fluctuation of the infant's body temperature.
- 2. To permit the use of oxygen.
- 3. To provide for the circulation of fresh air.
- 4. To protect the infant from infection from the air and from human contacts.

Different types of incubators are suited to the special needs of infants of varying degrees of prematurity. While the very immature infant may need a completely air-conditioned incubator, one who is more mature may need only a heated bassinet, an open-top incubator, or a heating hood, Nobel type.

Under conditions in which electricity is not available, or when it is impracticable to use electrically operated incubators, a simple boxtype of incubator can be used, heated by hot-water bags or bottles similar to that shown in figure 16.



Figure 17.—Emergency incubator ("animal carrier") used to transport premature infants by the Maternity Center Association, New York City (courtesy Maternity Center Association).

Transportation of a premature infant from the delivery room to the nursery or from the home to the hospital should be done in a heated carrier or "ambulance." Electrically heated "ambulances" are available commercially which plug into the dashboard light of a car. A simple type of carrier is a converted "animal carrier" available in pet stores. (See fig. 17.)

PURIFICATION OF AIR

Many studies have shown that pathogenic organisms are present in dust and that infection is spread in this way in hospitals. Various methods have been developed for lessening this danger (360).

The methods advocated especially for nurseries include:

- 1. Restriction of traffic to a minimum.
- 2. Exclusion of infected personnel.
- 3. Proper care of floors, furniture, and bed clothing.
- 4. Filtering the air as it enters the nursery, and sterilizing it.

All of these precautions should be taken in the care of premature infants.



Figure 17a.—Another view of Figure 17.

Restriction of traffic in and out of nursery

Studies made during the war showed a great increase in the bacterial count of the air with an increase in traffic in a given unit of living space. Traffic in and out of the nursery can be reduced by:

- 1. Provision of small nurseries so that one nurse can satisfactorily care for all of the infants in it. Standards call for one nurse for each four premature infants.
- 2. Provision at the bedside of closed containers for the clothing and utensils needed for each infant. This will protect the contents from dust and will also greatly reduce the number of times the nurse will need to go out of the nursery.
- 3. Provision of an examination and treatment room in close proximity to but outside the nursery proper, so that the physicians will not need to enter the nursery.

Exclusion of infected personnel

Physicians, nurses, maids, and orderlies who have any evidence of respiratory or skin infections should be excluded from the nursery and adjunct rooms. No house officers caring for infected patients should be on nursery duty.

Proper care of floors, furniture, and bed clothing

Floors should be wet mopped and furniture should be wiped with a moist cloth. Sweeping and dusting should *never* be done in the nurseries.

Oiling floors is advocated for controlling spread of dust-borne infection. The technique is presented in a British Medical Research Council report (228, p. 30). The oil used is "spindle oil" (a crude petroleum oil) which can be applied only to linoleum or wood floors. "It soaks too rapidly into concrete floors to remain effective. It damages rubber and certain composition floors. Oiled floors are not unpleasant in appearance and are odourless. Slipperiness of the floor may cause inconvenience for a few hours after oiling, but this rapidly passes off."

First, the floor should be scrubbed thoroughly with soap and warm water to remove old oil polish; it should be left to dry for 16 to 24 hours; then the spindle oil should be applied sparingly, with a mop-1 gallon per 800 to 1,000 square feet.

The British Research Council report goes on to state, "The effect of oiling lasts for increasing periods after each treatment. Applications should therefore be made two weeks and five weeks after the first oiling, and subsequently at seven-week intervals. If the floor must be washed in the meantime, it should be re-oiled when dry." Floors thus treated should not be polished.

For bedclothes, both blankets and linen, oil treatment is also advocated. The bacterial content of the air can be reduced by the use of an oil rinse after washing. Van den Ende and Thomas (364) state that a highly refined oil (white oil) should be used to avoid the "dermatitic factor." The use of this method has not been reported in care of bedding in infant nurseries, however.

Ventilation, and filtering and sterilizing of air

In air-conditioned nurseries and in incubators air change and air movement must be provided for, preferably by fresh air brought in from outside. Outside air should be filtered at the inlet to remove dirt and sterilized to prevent the spread of pathogenic organisms.

Ultraviolet light rays and glycol vapors or mists have been used to disinfect air.

A number of reports of the effectiveness of ultraviolet lamps in nurseries have been made. There are, however, certain disadvantages in their use. There is danger that the ultraviolet rays may cause injuries such as conjunctivitis and erythema, burns, and desquamation. The Council on Physical Therapy of the American Medical Association (20) states that such injuries can be avoided if lamps are installed at the proper elevation with the reflector adjusted so that the lamp does not shine in the faces of persons in the room; if the intensity is such that the lamp meets the minimum and maximum values specified by the Council; and if ceilings and walls are painted with a color which absorbs the ultraviolet rays. The Council requires that under

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suitable ventilating conditions the concentration of ozone near the occupants of a room shall not exceed 1 part in 10 million. Coblentz (21) points out that germicidal lamps are now available that are constructed so that ozone is not generated. In addition he states that "the total intensity of germicidal radiation emitted by each lamp in its fixture and the total number of lamp units used must exceed a minimum value in order to be effective in reducing cross infection. . ."

If germicidal lamps are used in attempting to reduce cross infection, they must meet rigid standards for safety and their efficiency must be tested often.

A number of studies have been reported in which glycol vapors have been used effectively to reduce cross infection. These studies are based largely on wartime experience in army barracks and in hospitals. Studies of use in newborn infants' nurseries have not been reported, however.

There are two forms of glycol that have been used, propylene and triethylene glycol. The use of these vapors has been found effective and harmless to the occupants of the areas in which they are dispersed. This method of air disinfection will no doubt become the method of choice. Practical methods for dispersion of the glycols and control of their concentration in the air are still being worked out. The bactericidal action of this vapor has been found most effective when the relative humidity was maintained at 40 to 50 percent.

Two recent reports (293 and 22) summarize present knowledge of the value of air disinfectants. It appears that the use of combined methods is necessary to obtain the best results. For example, Puck (279) and his coworkers report that the dust-preventive treatment of floors and bedclothes combined with triethylene-glycol vapor offers a promising means of controlling air-borne infection in hospital wards.

The latest report on this whole subject is that of the Subcommittee for the Evaluation of Methods To Control Air-borne Infections of the Committee on Research and Standards of the American Public Health Association (22). The following points are pertinent to nursery techniques:

- "1. The oiling of floors, blankets, and bedding has now developed to the point of practical application in the suppression of dust. Such measures constitute good housekeeping. They reduce bacterial contamination of the air, but there is as yet insufficient evidence that they prevent disease. Dust suppression should be applied wherever practicable in conjunction with ventilation, ultraviolet irradiation, and disinfectant vapors, when the latter methods are employed.
- **"2.** The available evidence strongly indicates that methods of air disinfection (ventilation, ultraviolet irradiation, and glycol vapors) are useful adjuvants to aseptic techniques in the reduction or elimination of air-borne infections in operating rooms and in contagious disease and pediatric wards. Installations are indicated under conditions where there has been demonstrated or there exists potentially a significant incidence of cross-infection or a serious risk to patients. It is essential that competent engineering supervision be available to insure the adequacy

of the original installation, to maintain its continued effectiveness, and to protect both personnel and patients.

"3. It is not yet possible to compare the relative efficiency of ultraviolet irradiation and glycol vapors. Only the former method has been developed to a point of practical application. Recent designs of glycol vaporizers and automatic control devices give promise that adequately controlled studies may be conducted in the near future. The relative merits of the two procedures will involve such problems as cost, safety, and the consistency of effective operation based upon long experience."

Identification

Identifying each newborn infant as the infant of a particular mother is a responsibility that every hospital must meet. The importance from a legal standpoint of the positive identification of each infant is obvious.

A number of methods for identification are in common use such as a string of beads, with the letters of the mother's name on them, placed around the infant's neck or wrist; adhesive tape marked with the mother's name in indelible ink and placed on the infant's back; or footprints of the infant made at birth.

The last-named method (footprinting) is the only absolutely reliable one and then only if it is properly done and the mother's fingerprint recorded at the same time and on the same record. One of the other methods for identification should also be used since the infant must be identified during its hospital stay as well as have a permanent record in the hospital files.

The Federal Bureau of Investigation (101) has pointed out that "The possibility of any two human beings having surface areas of skin on their fingers, palms, or feet which have exactly the same ridge characteristics is so remote that it is beyond the realm of probability. . . . The definitive formation of the ridges on the palms, fingers, and feet of human beings begins several months before birth and remains throughout the entire lifetime. These ridges are intact after death up until the time decomposition of the body takes place. . . . During the entire lifetime of a human being the ridges of his hands and feet remain exactly in their original formations and cannot be changed."

They also state that in infants it is easier to obtain footprints than finger prints and that the ridges are more pronounced on the feet than on the hands.

The Federal Bureau of Investigation suggests that a card similar to that shown in figure 18 be used for recording the infant's footprints and the mother's fingerprint in the hospital records.

The equipment needed to make these prints is simple and consists of the following:

- 1. Printer's ink (a heavy black paste).
- 2. A small piece of plate glass about 4 by 6 in.
- **3.** A roller about 3 in. long and 1 in. in diameter.

The following method for taking footprints is described in the bulletin (101): "In preparing to take a set of impressions a very small daub of ink should be placed on the inking glass and thoroughly rolled


until a very thin, even film covers the entire surface of the glass. To insure best results, the area of the feet to be printed should be thoroughly dried by wiping with a piece of gauze. The ink may be applied directly to the infant's feet from the roller but care should be exercised to insure a very thin film of ink on the portion of the foot to be printed. The inked area is then pressed firmly upon the surface of the card or certificate, but caution must be used to avoid either the foot or the paper being moved during the printing process in order to avoid smudging the print. Too much ink and too much pressure will result in a mere blot on the card, which of course is of no value for identification purposes." The Federal Bureau of Investigation recommends that the mother's right index fingerprint be made on the card together with the infant's footprints.

Some preparations other than printer's ink are available for footprinting infants. Only such preparations should be used as give assurance of permanence.

The bureau of identification of any police department will aid in instructing a nurse on how to make these prints and in reading them when the need arises.

Adair (3, pp. 826-827) gives the procedure used at the Chicago Lying-In Hospital for identifying the newborn infant as follows:

The cord, after being cleansed with alcohol, is tied with a sterile tape which has attached to it a small celluloid tag bearing the same number as the tapes to be used on the mother and infant.

The wrist is wiped clean and the sterile numbered tape is tied to it. A duplicate tape is affixed to the wrist of the mother.

The obstetrician calls aloud the sex and the number of the cord tie and tapes as they are affixed. (For example, Baby boy, Number 991.)

Later the infant's wrist tape is sewed and an adhesive tag with the infant's name, sex, number, and the physician's name is placed on the infant's back and left in place until the infant is discharged from the hospital. The maternal finger prints and infant palm prints are recorded on the labor record before mother and infant leave the delivery room.

Care of the skin

During and immediately after birth, the newborn infant's skin is invaded by bacteria. If the surface is intact the organisms may do no harm. Trauma to the skin may, however, lead to infection. Sources of trauma are forceps blades, rough handling of the infant during delivery, rubbing of the skin to remove vernix caseosa, and the use of soap and certain types of oil as well as rough or wet clothing. The premature infant's skin is especially susceptible to trauma and irritation.

Different techniques are used for care of the premature infant's skin in large maternity hospitals and premature-infant units. For example, Van Blarcom (362, p. 584) advises sponging the baby with warm olive oil (every day or every 2 to 3 days) "as he lies in his bed and with the least possible exposure and turning. . . . The buttocks are wiped with an oil sponge each time the diaper is changed." Zabriskie and Eastman (412, p. 512) recommend oiling the premature infant's body with warm oil. They say: "Oil to the skin is preferable to water because it prevents irritation and loss of heat." Hess and Lundeen (148, pp. 65, 66, 179) report that the routine at the Sarah Morris Hospital Premature Station is (1) an initial sterile mineral-oil bath; (2) a daily sponge bath until the cord is off and the navel is dry; (3) a daily bath of soap and water if the infant's condition warrants it, and a 40 percent alcohol rub following the bath. It is stated that the alcohol rub "does not cause drying of the skin" but that "if the infant's skin is dry, oil or cold cream may be applied immediately after the soap and water bath is given."

A few studies have been made to evaluate the various methods of care of the newborn infant's skin with a view to preventing infection, including the use of ammoniated mercury, various oils, sulfathiazole ointment, soap and water baths, and avoidance of all antiseptics and all bathing.

Sanford (304) reported the occurrence of "skin lesions" in newborn infants in six yearly periods during which different methods of treating the skin were used. The results of the study are shown in table 44. It can be seen that skin irritations occurred in 9 to 18 percent of infants regardless of the type of prophylactic treatment. Sanford (304) states that there was practical absence of pustules in the group of cases in which no antiseptic and no water or oil were used. "It is apparent, therefore, that the skin of the newborn infant, if left alone, and not injured by rubbing with an antiseptic, or irritated with washings, tends to clear itself and seems to give some immunity to infection."

V		Num-	Skin ir	ritation	Pustules	
1 ear	Type of treatment	infants	Number	Percent	Number	Percent
1930–31	2 percent ammoniated mercury at birth. Water thereafter.	539	56	13.9	18	3. 3
1931-32	Ammoniated mercury at birth. Olive	624	52	8.8	16	2.7
1932-33	No antiseptic at birth. Only olive oil used.	585	55	9.2	10	1.4
1933-34	No antiseptic at birth. Only commer-	530	73	15.8	14	2,8
1934-35	No antiseptic at birth. Olive oil and mineral oil	640	122	18.0	9	1.3
1935-36	No antiseptic at birth. Skin un- touched for 9 days.	609	61	10.0	1	. 16

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IVBLE	44	Sixtv-year	study	ot.	skin	lesions	ın	newborn	intants ¹

¹ Rearranged from Sanford's table.

Smith (327) reported that "during the last 2½ years 1,734 newborn infants have been cared for without any initial cleaning or bathing and without further bathing or oiling of the skin during their stay in the hospital (ten to fourteen days)." During this period there were only 2 cases of "even suspicious pyodermia." This study was made 10 years ago, but the author reports that the method is still in use.

MacLaren (216) studied the effect of 3 different types of treatment on the newborn infant's skin in the first 5 days of life in relation to the type of organism found in skin cultures. One group of 13 infants were given an initial soap and water bath from 6 to 12 hours after birth and one inunction of $2\frac{1}{2}$ percent ammoniated mercury; a second group of 14 infants an initial bath and one application of $7\frac{1}{2}$ percent sulfathiazole ointment; and a third group of 15 infants a soap and water bath on the first, third, and fifth days but no ointment.

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A variety of organisms were found in the cultures from the skin which MacLaren points out "must represent essentially harmless parasitic strains, since they were present on the skin in large numbers without causing any signs of disease. Therefore any attempt to evaluate the results of this study in terms of prevention of infective skin lesions rests upon the assumption that both virulent and harmless strains of the same organism would be affected alike by the treatment in question. . . On such a basis, and considering also irritating effects on the skin, the 3 types of treatment studied here would rank in order of preference: sulfathiazole first, ammoniated mercury second, and soap and water alone last." The author points out that sulfathiazole in the form of a $7\frac{1}{2}$ percent ointment "is not absorbed in detectable amounts" through the infant's intact skin nor does it produce skin irritation.

Weymuller and Ittner (392) report 2 years' experience (1942-44) with the prophylactic use for 3,205 infants of 15 gm. of a 5-percent sulfathiazole ointment prepared "in an oil-in-water-type emulsion base." The incidence of pyoderma in this period was only 0.12 percent (4 cases) compared with 1.23 percent in 1930-40 and 1.14 percent in 1940-42.

In order to determine possible toxic effects or sensitization, the sulfathiazole levels in the blood were determined 78 times at varying periods after the inunctions. The average level found was 0.5 mg. per 100 cc. (range from trace to 1.7 mg. per 100 cc.). The authors considered these levels "insignificant." Blood counts and urinalyses showed no abnormalities. Forty-nine of the 3,205 infants were readmitted to the Long Island College Hospital for serious illnesses which required full dosages of sulfonamide compounds. Sulfathiazole was used in treating 43 of them. "No instance of sensitization to sulfonamide compounds was encountered."

The authors point out that their study does not prove conclusively that this method of skin prophylaxis "will always be equally effective and productive of no untoward results." Their experience was relatively short, the hospital stay of the infants was between 7 and 10 days rather than the usual 2 weeks; and they recognize that pyoderma is characterized by periods of very low incidence, even though no special control measures are taken.

Although good results are reported through the use of sulfathiazole ointment for skin prophylaxis no reference is made to the inclusion of premature infants in these studies. For these infants strict aseptic technique, without special prophylactic treatment and without bathing, would appear to be the method of choice because it combines effectiveness in prevention of infection with reduction in the amount of handling necessary. (See also Prevention of Impetigo, p. 260.)

Clothing

The subject of clothing for premature infants has been given very little attention by physicians. It has been largely relegated to the field of nursing care. Statements made in the medical and nursing literature concerning suitable clothing for these infants appear to be based largely on clinical impressions and customs. Scientific studies are needed to determine, in relation to stabilization of body temperature, the effect on the clothed as well as on the unclothed infant of environmental conditions automatically controlled; i. e., in incubators. The chief role of clothing is to prevent loss of heat by insulating the body from changes in environmental temperature.

Recently Gesell (110) has pointed out that the type of clothing may have a psychologic effect on the premature infant.

In medical and nursing textbooks two types of clothes are usually advocated for premature infants—temporary or "emergency" clothing, to be used at the time of birth and in the earlier neonatal period, and permanent clothing.

EMERGENCY CLOTHING

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In regard to "emergency" clothing, according to Van Blarcom (362, p. 576), the premature infant should be "entirely wrapped in cotton batting or flannel or enveloped in a quilted garment, with hood attached, made of flannel or cheese cloth and cotton batting."

Sellew (313) advises a premature jacket "which may be of soft flannel in the form of a cape" with a hood attached.

Zabriskie and Eastman (412, p. 515) state that "if the baby is not in an incubator, he is dressed in a jacket of cotton and gauze or flannel."

Hess and Lundeen (148, p. 67) advise that at birth the infant should be received into a warm blanket and immediately placed in a heated basket or heated bed. In caring for small prematures, for temporary emergency use, a sterile cottonpack which completely envelopes the infant except for the face, may be used. An improvised jacket, preferably of flannel, may be placed on the outside of the cotton to hold it in place. An easily changed pad of cotton or gauze combination may be applied to the genital region and anus.

Gesell's (110) observations of premature infants have led him to conclude that close-fitting clothing provides "the tactile and thermal snugness" which the infant "craves" because he is deprived at birth of the "snug investment of the uterus."

PERMANENT CLOTHING

In different hospitals the clothing actually used for premature infants varies greatly. In some hospitals the infants in air-conditioned incubators are left nude; in others they are clothed. In some, infants in bassinets are dressed in shirts and gowns and covered with tightly tucked-in blankets. No data are available to indicate that any one type of clothing is preferable to another. In general the clothes should be light in weight, warm, soft and smooth, and so constructed that free movement is permitted, and so that the clothes may be easily put on and taken off without excessive handling of the infant. Since Day found that exposure of one small part of the premature infant's body (a foot) resulted in body-temperature changes, the whole body, except, of course, the face, should probably be covered. Sleeves should be long enough to cover the infant's hands, and the gowns long enough to cover the feet. (Personal communication from Richard M. Day, M. D., Babies Hospital, New York.)

Hess and Lundeen (148, p. 67) describe the clothing used in the premature unit of the Sarah Morris Hospital as follows:

With open-type heated beds, all garments next to the body, except diapers, should be made of light-weight flannel. A complete outfit for the use of an infant in an open-type heated bed should contain:

Four undershirts with blind sleeves (light-weight wool flannel).

Four overjackets (French pique or cotton flannel).

Four pinning shirts (French pique or heavy diaper material 24 by 28 inches).

Three light woolen blankets, 1 yard square.

They recommend, for temporary use in place of a diaper, an easily changed pad of cotton; for permanent use, diapers of fine birdseye, 10 by 20 inches. They describe this as a "small triangular diaper" which is fastened "with a large safety pin, and the flap is placed over the pin."

Unless the infant is very small, only the outer shirt is worn in the summertime and in a warm oxygen chamber. The shirts must reach to the hips, so that the diaper can be wrapped over the lower border.

Psychologic aspects of care

The emotional life of premature infants has received practically no consideration in the development of methods for their care. These infants suffer from separation from their mothers, the enforcement of rigid isolation, and routine methods of care just as do full-term infants.

Jackson (169) has pointed out that, in the effort to reduce infant mortality—efforts that have been gratifyingly successful—hospital procedures have been developed which have disregarded "essential psychological needs of both mother and child." Spock (333, p. 363) has pointed out that many of the behavior problems of later infancy and childhood have been traced to the patterns established in the early days and weeks after birth. "Serious behavior problems seldom arise abruptly in later childhood." Feeding problems are among the commonest behavior disturbances, he states, and "in the neonatal period are more common in premature babies because of the inverse ratio between the baby's size and the mother's anxiety."

As one measure to prevent psychologic maladjustments between mother and full-term baby, it has been suggested that closer motherbaby relationships be established in the lying-in period. This may be effected by making arrangements to keep the newborn baby in the mother's room, so that she may hold him, nurse him, and care for him; by maternal nursing; and by a "flexible self-demand" feeding time (318 and 319).

Unfortunately these methods of care, which have been put in use and found to be successful in the care of full-term infants, are difficult to apply to the care of premature infants in the neonatal period. It is desirable, however, to take cognizance of the emotional needs of premature infants and to make such adjustments, with these needs in view, as will not menace their physical well-being.

Handicaps in meeting the psychologic needs of premature infants are:

1. The need for controlled environmental temperature and humidity and for an increased oxygen supply in many cases, which makes isolation in a special air-conditioned nursery or an incubator necessary.

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- 2. The high susceptibility to infection.
- 3. The functional immaturity of the infant which makes skilled care in handling and feeding a necessity.
- 4. The inability of most premature infants to nurse at the breast in the neonatal period.
- 5. The inability of premature infants to demonstrate a "demand" for food because they do not cry vigorously and often do not cry at all.
- 6. The prolonged hospital stay that is required for most of these infants.

The emotional life of the infant is closely related to the emotional life of the mother. The mother of a premature infant is handicapped because:

- 1. She cannot see her infant or make normal contacts with him because of the special environmental conditions under which he must be cared for. This results, in most instances, in anxiety on her part.
- 2. She cannot nurse her baby until he is strong enough to nurse which may be a period of weeks.
- **3.** When she sees him he is usually in an incubator and being cared for by a nurse in cap, gown, and mask. She immediately develops a feeling of inadequacy as to her ability to care for him.
- 4. She usually has to go home without her baby which may in itself develop in her an abnormal emotional state.

A concerted effort should be made to counteract these adverse influences and to provide for a more normal situation for both mother and infant by:

- 1. Encouraging the mother to maintain her breast-milk supply with a view to nursing her baby as soon as he is strong enough.
- 2. Showing the baby to the father, and to the mother as soon as she is able to be up in a wheel chair.
- **3.** Allowing the mother to hold the baby as soon as he can safely be taken from the incubator.
- 4. Demonstrating to the mother, while she is still in the hospital, the methods of care.
- 5. Discontinuing the artificial environment of the infant at the earliest time compatible with his welfare by: (1) transferring the infant from an incubator to a heated bassinet and then to an ordinary bassinet; (2) having the nurse hold the infant during bottle feeding; (3) putting the infant on a "self-demand schedule" as soon as he is able to show his hunger by crying provided the physician is sympathetic with this regime, and there is no contraindication from the point of view of the mother's or infant's physical condition, the mother's mental attitude, or the social situation (361).

After the mother is discharged she should be encouraged to visit the infant daily and, when it is considered safe, she should be allowed to hold him. An effort should be made to maintain the milk supply of every mother of a premature baby, so that eventually he may be able to nurse. Gordon, Levine, and McNamara (121) and Powers, who believe that special cow's milk mixtures are in general the best food for small premature infants, have recognized the psychologic importance of maternal nursing. The former suggest that large premature infants receive milk from their own mothers when it is easily obtainable and nurse at the breast as soon as they are able. Powers (277) says: "When the premature infant attains a degree of maturity commensurate with nursing at the breast he should be given that privilege. Maternal lactation can be maintained in favorable cases with effort on the part of the mother and encouragement on the part of the physician."

If a premature infant is very small and feeble and needs prolonged hospital care, maternal nursing, of course, may not be possible and the mother must then be taught how to make up the feeding mixture and give the feedings to the infant.

Consideration should be given to the mother's intelligence and the situation in the home with a view to making the period of hospital stay for the infant as short as is consistent with safety. (See Criteria for Discharge from Hospital Care, p. 113.)

A plan may need to be worked out by the hospital for cooperation with public and private nursing and welfare agencies to prepare the home for the infant and to arrange for preventive and curative medical services and follow-up examinations.

In addition to these arrangements for the infant's physical wellbeing the hospital and later nurses visiting the home should undertake to allay the mother's anxiety about the infant and encourage her, when he has reached the status of a full-term infant, to handle him like one. Washburn says she should be made to realize that his outlook is now good and that any special handling resulting from continued anxiety on her part is both unnecessary and undesirable. (Personal communication from Alfred H. Washburn, M. D., Child Research Council, University of Colorado School of Medicine, April 8, 1948. See also Mental and Emotional Development, p. 87.)

Summary

RESPIRATION AND OXYGEN THERAPY

A much larger proportion of premature than of full-term infants have respiratory difficulties in the early neonatal period, particularly at the time of birth.

There are a number of causes of delayed onset of respiration in premature infants. Some of these causes are related to the immaturity of the nervous system and of structures that play a secondary role in respiration; some are related to such factors as birth injury, analgesics and anesthetics given to the mother during labor and delivery, abnormalities of the lungs or compression of them by thoracic or abdominal viscera and other conditions, interfering with the oxygen supply of the fetus.

The mechanisms by which extrauterine respiration is established are not fully understood. From a large number of studies made on animals and some on human infants it has been shown that sensory stimuli, changes in the oxygen and carbon-dioxide relationships in the blood, and possibly the presence in the blood of an adequate amount of an enzyme carbonic anhydrase which aids in the utilization of oxygen, all play a part.

Regardless of the cause of delayed or inadequate respiration, the infant is in a state of anoxia.

Many methods for initiating respiration have been advocated but exact data in regard to their effectiveness and relative merits are not available.

Steps to initiate respiration must be taken quickly and under conditions favorable to the general welfare of the premature infant. These conditions are skilled medical and nursing care, a warm environment, and suitable equipment in readiness for use. There should be provided a warmed blanket, an incubator, a hypodermic set, suitable apparatus for suction of the mouth and upper respiratory tract and for administering oxygen.

The methods to be used to resuscitate infants who have never breathed differs from the methods used for those who have breathed but breathe inadequately.

For infants that fail to breathe spontaneously, the first step is clearing the mouth and respiratory tract, then administration of oxygen. Oxygen will not be utilized, however, unless administered under conditions of alternating negative and positive intrathoracic pressure so that a resuscitator must be used or, in an emergency, mouth-to-mouth insufflation.

If a resuscitator is used it should be provided with a hand-controlled shut-off device and rhythm regulator. The rhythm should be about 12 to 15 inflations per minute; pressure should be controlled mechanically at a maximum of about 16 mm. of mercury and set usually at 12 mm. The oxygen-air mixture (38 to 42 percent oxygen or even higher) should be controlled as to rate of flow, at about 4 meters per minute. It is well to have a suction device as a part of the resuscitator.

The Flagg method of direct tracheal insufflation after catheterization may be used if the operation is performed by one qualified to use this technique and experienced in using it for treatment of small premature infants.

Caffeine sodium benzoate, ¹/₄ to ¹/₂ gr., or epinephrine, 1 to 2 minims of a 1 to 1000 solution, may be used as a respiratory or a cardiac stimulant, but alphalobeline, coramine, and metrazol should not be used as. they are dangerous. There is no advantage and considerable danger in applying rhythmic hand pressure to the chest.

In cases in which respirations, after they are initiated, are difficult to maintain or inadequate, oxygen should be given and continued as long as indicated by the type of respiration and the degree of cyanosis. A resuscitator should **not** be used when the infant is breathing spontaneously, even if respirations are shallow and irregular.

Oxygen is of great value in the treatment of premature infants. Indications for its use are failure of respiration, cyanosis from any cause, and a general feeble condition.

Oxygen should be given ordinarily in a concentration of 38 to 42 percent but may be given in concentrations as high as 80 percent or even higher.

There are possible dangers in oxygen therapy. Symptoms of pulmonary irritation have been observed in animals living in high concen•

trations of oxygen. It is probable that a relatively high humidity, such as should be maintained in air-conditioned rooms and in incubators, is a safeguard against possible irritation of the lungs by high oxygen concentrations.

To administer oxygen requires suitable apparatus to measure and regulate the oxygen flow and pressure. The gas should be bubbled through water to moisten it.

There are several methods that are effective for delivering oxygen to infants over relatively long periods of time:

- 1. The open-box method in which the gas is diffused from a tube in close proximity to the infant's nose.
- 2. Closed method (oxygen tent). There are types of oxygen hoods that are transparent which may be used over an ordinary bassinet. Most incubators are so constructed that they may be used as oxygen tents. They **must**, however, be so constructed that there is no fire risk. Unless the incubator is air-conditioned there is some danger from overheating when oxygen is continued over long periods and provision should be made for cooling.

In addition to these measures, repeated small transfusions of blood have been found to have a beneficial effect on the respiration of these infants.

ENVIRONMENTAL CONDITIONS

In the uterus the body temperature of the fetus is maintained at an optimum level by the metabolic relationships between mother and fetus and by the protection of the amniotic fluid within the uterine walls.

At birth the full-term infant is able to make a rather rapid adjustment to the environment, but the premature infant is ill-prepared to do so. This is due to a number of factors, among them poor development of sweat glands; inadequate subcutaneous fat; a surface area relatively great in proportion to body weight, and a low total catabolism.

Calorimetric studies have been made by Day and coworkers of the mechanisms involved in the premature infant's inadequate temperature control. They found that to maintain a uniform body temperature the infant needs a carefully regulated environment. The infant's body temperature responds to hot or cool conditions. Hyperthermia is related to inability to sweat; hypothermia, to a relatively large surface area, thin subcutaneous tissues, low metabolic rate, and diminished muscular activity. Rectal temperatures of most of the premature infants studied were found to be below 37° C. (98.6° F.), which suggests that the normal rectal temperature of premature infants may be low.

The importance of providing suitable environmental conditions has long been recognized. The degree of heat and amount of relative humidity considered optimum are based on studies made many years ago. The studies showed that the relative humidity should be about 65 percent with a room temperature ranging from 75° to 100° F. When nurseries are heated by radiators and ventilated by natural means this degree of humidity cannot be maintained except by an automatically controlled humidifying device. When air-conditioned nurseries are not available suitable temperature-humidity relationships can best be maintained by the use of incubators. It may be necessary, even in air-conditioned nurseries, to use incubators for the smaller infants.

Incubators should be so constructed that the infant is readily visible and easily tended, and the mechanism of operation dependable and relatively simple. Adequate ventilation should be provided for. Incubators should meet standards for safety. Every precaution should be taken against any fire hazard, particularly when oxygen is being administered in an incubator.

For transporting a premature infant from home to a hospital, or in the hospital from the delivery room to the nursery, a carrier should be provided that is so constructed that suitable environmental conditions are maintained.

Many studies have shown that pathogenic organisms are present in dust and that infection is spread by dust in the air.

To lessen the danger of this source of infection of infants in nurseries, it has been recommended that traffic in and out of nurseries be reduced to a minimum; that personnel with infections of the skin and respiratory tract be excluded; that sweeping of floors and dry dusting of furniture be forbidden. Furniture should be wiped with a moist cloth and floors wet-mopped or oiled. Oiling of bed clothes will also tend to decrease the spread of organisms by dust.

The bacterial content of the air can be reduced by the use of ultraviolet lamps or aerosols. Methods for glycol vaporization and for automatic control of dissemination of the vapor in nurseries are not yet perfected.

Studies have shown the combined use of oil on floors and bed clothes and of aerosols is the best means for controlling air-borne infections in hospitals.

IDENTIFICATION

Identification of each newborn infant as the infant of a particular mother is essential from a legal standpoint. The identification should be established at the time of birth. The infant should be tagged with the mother's surname and a birth number which is recorded on the mother's record form. At the time of birth, the infant's footprints and the mother's fingerprint should also be recorded on the same form. This is the only absolutely reliable evidence that an infant is the infant of a particular mother. With this record identification can be made at any time in later life. The infant should also be identified for daily care.

CARE OF THE SKIN

The premature infant's skin is especially susceptible to trauma, which may lead to infection. Various techniques for routine care of the infant's skin include the use of oil, soap and water, and alcohol. Studies of the relative value of these methods for premature infants have not been found.

A number of studies have been made to evaluate different methods of preventing skin infection. In a comparative study of several of these methods the lowest incidence of pustules was found when no antiseptic and no oil or water was used. According to another report, when this method was used, there was a very low incidence of pyoderma—only 2 cases in 1,734 newborn infants. This study was published in 1938, but the method is reported by the author to be still in effective use.

In a more recent study the prophylactic use of sulfathiazole ointment is reported to have been found effective in reducing the incidence of skin bacteria and skin irritation without subsequent sensitization. Other reports caution against its use because of possible sensitization and other harmful results.

For premature infants, to prevent trauma of the skin and excessive handling, the best method of prophylaxis would seem to be strict asepsis without bathing and without the use of antiseptic ointments.

CLOTHING

The types of clothing recommended for premature infants vary widely. The recommendations are based on clinical experience and custom.

Scientific studies are needed to determine the best way to clothe premature infants of varying degrees of prematurity under different environmental conditions. Psychologic aspects of clothing for these infants may be important.

The chief role of clothing is to prevent loss of heat from the body by insulation.

Two types of clothing are usually described—temporary or emergency and permanent clothing. The former consists of a gauze-covered quilted cape or envelope with hood or a similar covering of flannel. This type of emergency garment is usually not necessary if an incubator is provided in the delivery room.

Permanent clothes should be such as are suitable to the infant's condition and to the external environment. The clothing should be adequate to conserve the infant's body heat, made of material that will not irritate the skin, and so constructed that activity will not be interfered with and the clothes may be easily put on and taken off without overhandling of the infant.

For the diaper area absorbent pads are suitable for the smaller infants; for the larger ones diapers of soft absorbent material and of appropriate size may be used.

PSYCHOLOGIC ASPECTS OF CARE

The satisfaction of the emotional needs of the premature infant is difficult because of his physical need for a controlled environment, special handling and feeding, and in many cases, prolonged stay in the hospital. On the mother's part, lack of normal contacts with the infant, such as nursing at the breast, may give rise to feelings of inadequacy and anxiety. Measures to counteract these disadvantages are: Encouraging the mother to maintain her breast-milk supply so that she may nurse the infant later, instructing her in methods of care, allowing as much contact between parents and infant as the infant's condition permits, and making the infant's hospital stay as short as is compatible with safety in consideration of his condition and the home The hospital may need to arrange with community agensituation. cies for follow-up care in the home. Instruction of the mother both during her hospital stay and in the home should aim to allay anxiety and encourage her to treat the infant like a full-term infant just as soon as his development permits.

NUTRITION

Nutritional handicaps

The feeding of premature infants is complicated because the various mechanisms for ingestion and digestion of food are not fully developed. The more immature the infant, the more difficult is the feeding problem. In addition, the needs for rapid growth in an infant born with low stores of minerals and vitamins must be met in the presence of the following handicaps:

- 1. The sucking and swallowing reflexes may be absent or sluggish.
- 2. The small capacity of the stomach leads to distention and vomiting.
- 3. The gastric acidity is low.
- 4. The absorption of fat is poor.
- 5. The digestive enzyme system is incompletely developed.

Not all infants weighing 2,500 gm. or less show these handicaps; and since a birth weight of 2,500 gm. or less is an arbitrary standard of prematurity, infants as they approach this weight give evidences of being more or less mature. Some infants that do not yet weigh 2,500 gm. may behave as mature infants so far as their digestive tract is concerned, and others who have reached this weight may still have to be treated as somewhat immature.

Only in recent years has research begun to throw light on these handicaps and their relation to the peculiar nutritional needs of premature infants. These needs have been found to call for special proportions of protein, fat, and carbohydrate and ample supplies of minerals and vitamins. Human milk has long been considered the ideal food for premature infants and essential for their proper nutrition. It has been used for many years to feed these infants, sometimes with modifications on various theoretical bases to meet the premature infant's special nutritional requirements. But the scientific evaluation of human milk compared with cow's milk as a food for premature infants has been made only recently. More extensive research is needed to cover all phases of premature-infant nutrition and more intensive research, to confirm tentative and resolve conflicting conclusions. Some guiding principles for feeding premature infants have been established, however. The following pages will review the results of studies that have been made and will present recommendations for feeding premature infants that will put these results into practice.

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Nutritional requirements

PROTEIN REQUIREMENT

The premature infant has special need for protein because of his low stores at birth and his extremely rapid growth. The capacity of these infants to absorb and retain nitrogen from either human milk or cow's milk is efficient (122). The infants studied by Gordon and Levine (119) absorbed approximately 90 percent of the protein even when they were given almost twice the amount found in cow's milk, and in one case, more than three times the amount. The percentage of utilization was higher for premature infants than for full-term infants under comparable conditions and was higher the smaller the infant at the time of observation. "The evidence suggests that the heightened retentions in young children are related to their increased rate of growth (p. 470)." However, premature infants fed cow's milk of high protein content (5.0 gm. or more per kg. of body weight) were found by Levine and his associates (206 and 74) to have a defect in the metabolism of certain amino-acid constituents of protein for which vitamin C was a specific corrective. The high-protein diet needed by premature infants therefore calls for an increased daily amount of vitamin C. (See p. 160.)

A number of recent studies indicate that adequate protein in the diet plays other important roles, such as promoting hemoglobin formation, increasing antibody formation, and acting enzymatically to promote utilization of the vitamins of the B complex. Some of these effects have been found to be due to the action of specific amino-acids.

Block and Bolling (41) made a study of the comparative value of the proteins of human milk and cow's milk in terms of their content of 12 amino-acids. They comment that "the former impression, gained primarily from clinical studies, that human-milk proteins are superior, is no longer held by some authorities." Their own results showed marked differences between the proteins of human milk and those of cow's milk only in two amino-acids—cystine (human milk higher) and methionine (cow's milk higher), "the essential acid being methionine. However, the total of the sulphur amino-acids of both human-milk and cow's milk proteins is approximately equal." The

TABLE 45Daily allowance of protein recommended for infants 6-8 months of age
by the Food and Nutrition Board, National Research Council,¹ and
suggested modifications for premature infants and for full-term infants
under 3 months of age (Levine)

Age and weight	Gm. per kg.	Gm. per lb.	Percent of total cal- ories (aver- age)
Infants 6-8 mos. of age (Food and Nutrition Board, National Re- search Council). Premature infants: 1 week-1 mo. of age: Weighing less than 2,000 gm. (4 lb. 6 oz.) Weighing 2,000 gm. or more 1-3 mo. of age Full-term infants: 2 days-3 mo. of age	¹ 4. 0–3. 0 6. 0–4. 4 5. 0–4. 4 4. 4–3. 3 4. 4–3. 3	2. 7-2. 0 2. 3-2. 0 2. 0-1. 5 2. 0-1. 5	17 15 13 13

¹ National Research Council, Food and Nutrition Board: *Recommended Dietary Allowances*. Reprint and Circular Series 115, January 1943 (p. 2). In the latest edition of this publication (242) the protein allowance was given as 3.5 gm. per kg.

authors conclude: "It would appear, from a consideration of aminoacid data only, that human-milk proteins are **not** nutritionally superior to the proteins of cow's milk."

The daily allowances of protein for premature infants at specified ages and for full-term infants 2 days to 3 months old suggested by Levine (201) are shown in table 45. (See also table 47, p. 171.)

FAT REQUIREMENT

The infant that is premature usually has difficulty in absorbing fat. As is shown in table 46 (p. 168), the percentage of fat in human milk and in cow's milk is approximately the same (3.5 percent). It has been frequently stated that the fat of human milk is more easily digested than that of cow's milk because the fat globules of human milk are smaller than those of cow's milk and therefore more readily accessible to the digestive juices. Holt and associates (156) found, however, that accurate measurements show no marked differences in the size of the fat globules of human milk and cow's milk, the variations between breeds of cows and between individuals being greater than those between species. Moreover, these authors also found no evidence that the infant has difficulty in digesting milks with larger fat particles. Ease of absorption was dependent, rather, upon chemical com-In feeding tests with 17 fats (including 5 from proprietary position. infant foods) on normal male infants between 6 weeks and 8 months of age, the average percentages of absorption of those receiving olive oil and soy-bean oil were considerably higher than the average for those receiving butterfat and were somewhat higher than the average for those receiving human-milk fat.

Tidwell and associates (353) then made 22 experiments on 9 healthy premature infants to whom various fats were given and studied the fat absorption of 4 of these infants fed different types of fat in consecutive periods. Their figures show that soy-bean oil was retained in a much higher percentage (average 83.1 percent) than butterfat (average 58.3 percent), not only in the averages reported but in the individual records, but the authors comment that "it is possible that the infants studied on soy-bean oil were better fat absorbers" (2 of them were identical twins). The percentage of retention of olive oil (average 72.4) was also markedly higher than that of butterfat. The authors concluded that the infants absorbed both olive oil and soybean oil ("fats containing predominantly unsaturated fatty acids") "far more completely" than butterfat and that improvement in the infant's nutrition was "often reflected promptly in the weight curve."

Gordon and McNamara (123) also found that premature infants tend to have difficulty in fat absorption. In their studies (p. 331)premature infants fed "customary cow's milk mixtures" or human milk (boiled) tended to excrete an excessive amount of fecal fat when comparisons were made with fecal fat excretion of full-term infants on similar diets. When premature infants were fed on relatively low-fat cow's milk mixtures (half-skimmed milk) the fecal fat excretion tended to be decreased to the level observed for full-term infants fed unskimmed cow's milk mixtures. The authors state (p. 340) that they have not obtained information from their studies as to the cause of the premature infant's deficiency in the ability to absorb fat.

These authors in addition made 22 observations on 17 premature infants fed cow's milk mixtures in which olive oil was substituted for

milk fat. The fecal fat excretion of 6 full-term infants on similar feedings was also studied. The authors concluded (**p. 333**): "The marked variation in the ability to absorb fat of the different infants and of the same infant at different ages . . . makes computed averages of doubtful value and vitiates any conclusions drawn from the present data on the relative digestibility of milk fat and olive oil by premature infants." Later the feeding of butterfat and olive oil to a small group of premature infants in successive periods led to the conclusion that they did not absorb olive oil better than butterfat. (Personal communication from Harry H. Gordon, M. D., Colorado General Hospital, Denver.)

The clinical significance of the finding that premature infants have poor fat absorption is brought out by Gordon and McNamara (123, **p. 343).** If a premature infant, particularly one who is small or young, fails to gain on a diet of human milk or customary cow's milk mixture which supplies approximately 120 calories per kg. (55 calories per lb.) and which supplies 35 to 50 percent of the calories as fat, "it would seem more logical to decrease the amount of fat in the mixture by substituting isocaloric amounts of protein or carbohydrate rather than to increase the total caloric intake." A low intake of fat, however, is an added reason for early administration of large amounts of vitamins A and D, and "the higher carbohydrate intake may indicate higher requirements for thiamine." (See pp. 155, 158, 162.)

Powers (277) states that knowledge of the metabolic function of fats is not complete, but, aside from their association with vitamins, which can now be supplied in other forms, "fats are intimately associated with water, mineral, phospholipid, and sterol metabolism." According to Holt and associates (156, p. 478), "Fat-poor diets tend to produce loose, fermentative stools; at times they appear to bring out allergic manifestations." Gordon and McNamara (123, p. 343) point out, however, that in their studies of premature infants no evidence was obtained that the amount of fat absorbed by the infants fed the half-skimmed milk mixtures was inadequate; the needs for essential fatty acids appeared to be met, the infants gained well, and they did not develop eczema during their stay in the hospital.

The majority of premature infants, as they progress toward maturity, develop ability to absorb fat and thrive on either whole cow's milk (liquid, dried, or evaporated) or human milk. Moreover, some premature infants of low birth weight appear to tolerate from the beginning feeding mixtures that have the fat content of whole milk. It is safer, however, to assume that the defect in fat absorption is present in all small premature infants and to give a feeding mixture low in fat in all such cases.

CARBOHYDRATE REQUIREMENT

Adequate amounts of carbohydrate are necessary in the infant's diet not only to provide calories but, according to Davison (78, sec. 213), to maintain water balance, to complete oxidation of fat, to prevent ketosis, and to maintain the glycogen stores in the liver.

The premature infant tolerates carbohydrate well. As Smith (322, p. 215) points out, "Since the fetus apparently utilizes carbohydrate as its main, if not its only, source of energy, it is understandable that dextrose is handled efficiently once it has reached the blood.... The apparatus for the digestion of disaccharides (milk

and cane sugars) and that for monosaccharide (dextrose) absorption, is in satisfactory working order very soon after birth." The bloodsugar levels of infants fall in the immediate postnatal period, and the level reached is lower in the premature than in the mature infant. In Smith's opinion "newborn infants in general show so few symptoms of hypoglycemia that a peculiar neonatal tolerance to a low blood sugar may be suspected." (See Hypoglycemia, p. 314.) However, the premature infant's tolerance makes carbohydrate, as well as protein, a logical caloric substitute for the fat that the small premature infant does not tolerate well.

Human milk has a higher carbohydrate content than cow's milk (7.50 percent compared with 4.75 percent). It is customary in feeding full-term infants on cow's milk to supplement with carbohydrate up to the content of human milk. Clinical experience shows that premature infants tolerate well an even larger amount of carbohydrate (about 10 percent). (See p. 172.)

CALORIC REQUIREMENT

Metabolic studies of premature infants have shown that even with due consideration of individual differences, the caloric requirements are relatively low. Gordon (116) has observed that in the first 2 days of life the basal metabolism is only 40 to 50 calories per kg. per day, "activity is minimal, and the quotas for fecal loss and specific dynamic action which depend on the food intake are small," so that the caloric intake is of no real concern. After this period, according to Gordon and Levine (119), "the low basal metabolism and low activity quota of some premature infants, characteristic for the first 2 weeks of life, are adequately covered by intakes well below 120 calories per kg. Premature infants who do not gain on such intakes of customary cow's milk mixtures usually fail to do so because of excessive loss of calories as fecal fat. Dietary calories should not be increased; dietary fat, rather, should be reduced . . . ," with compensatory substitution of calories from carbohydrate.

Gordon and his coworkers (120, p. 1202) have concluded from calorimetric studies of 11 healthy male premature infants ranging in age from 10 to 44 days and in weight from 1,543 to 2,564 gm. when the observations started, that after 2 weeks of age "diets which supply approximately 120 calories per kg. per 24 hours may be considered adequate under customary environmental conditions to cover the maintenance energy requirements and to provide a surplus for satisfactory weight gain in healthy premature infants." Since the basis for judging "optimal growth" for premature infants is not yet established, the authors give as one criterion for a "satisfactory weight gain" the rate of weight gain in utero, calculated on the basis of figures from Streeter and from Scammon and Calkins, as 15 gm. per kg. per day for infants of 1,000 gm. and 10 gm. per kg. for infants of 2,000 gm. For the 11 infants studied, averaging 2,294 gm. in weight, the average daily weight gain on a diet ranging from 104 to 144 calories was 16.2 gm. per kg. The authors emphasize the necessity for individualizing the feeding of premature infants in accordance with variations in basal metabolism, age, environmental temperature, activity, and ability to absorb fat. Levine and Gordon (204) also emphasize the desirability of giving premature infants the minimum amounts of food and fluid that result in satisfactory gains in weight.

As the weight of the infant increases the caloric value of the feeding must be increased so as to keep the number of calories per kg. constant. Gordon (118, p. 324) suggests that if during the first 10 days of life, a premature infant is taking his feedings well, "a schedule calculated to increase the caloric intake each day from birth by approximately 10 or 15 percent of the final total will gradually bring the intake to the desired level" of 120 calories per kg.

Hess and Lundeen (148, pp. 100, 102) also believe that the premature infant "does best if fed the smallest amount of food on which it will gain weight." They have had many years of experience in feeding premature infants on human milk, to which it is their custom to add skimmed lactic-acid milk on the fourth or fifth day for premature infants weighing 1,250 gm. cr more. These authors report that they have not found it necessary to give more than 100 calories daily per kg. of body weight until the infants are more than a month old. After that period they increase the feeding to 110 or 120 calories per kg. if necessary. They say that in their clinic the infants "usually require from 60 to 100 calories per kg. of body weight per day to gain weight."

(For composition of milk mixtures for feeding premature infants see table 47, p. 171.)

FLUID REQUIREMENT

An adequate supply of water is essential to the maintenance of health and nutrition. Powers (277) states: "In infant feeding water should be regarded . . . as one of the essential structural elements of the body. Water is necessary also in the regulation of temperature and in the assimilation and elimination of metabolic products." The composition of the blood and the electrolyte balance between extracellular and intracellular fluids are also related to the water intake and output of the human organism. Abnormal retention or loss of water by the body or the administration of various solutions for therapeutic purposes may upset the electrolyte equilibrium with serious results. (For table of various fluids used for parenteral administration, see appendix 7, p. 388.)

Water accounts for a large proportion of the body weight, and this proportion is greater in the fetus than in the infant born at term. (Water comprises between 82 and 83 percent of the weight in the 7- and 8-month fetus; approximately 75 percent in the infant born at term.)

The problem of the hydrolability of newborn infants, especially premature infants, and their tendency to dehydration have been recognized. This problem is greater in premature infants than in full-term infants, partly because of inadequate kidney function.

Levine and Gordon (204, p. 305) have made water-balance studies of 13 premature infants. They found that with the daily fluid intake below 95 cc. per kg. there was a negative water balance with resultant dehydration and fever. With fluid intakes between 124 cc. and 167 cc. per kg. positive water balances were found. The infants "retained in their bodies average daily amounts of water totaling between 19 and 24 gm., the extra water of the higher intakes merely being eliminated as extra urine." On the basis of these experimental observations and their belief that "it is better practice to feed minimal amounts consistent with satisfactory progress" Levine and Gordon

recommend that premature infants be given milk mixtures "rarely, if ever, exceeding 150 or 160 cc. of fluid per kg. per day."

MINERAL REQUIREMENTS

Calcium and phosphorus

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Because of incomplete antenatal storage and the demands of rapid growth the premature infant has greater need for calcium and phosphorus than the full-term infant.

Hansen (136, pp. 53-88) states the functions of calcium and phosphorus as follows:

Calcium in the diet (1) furnishes important material for structure of bones and teeth and (2) plays a role in (a) muscle contraction, (b) control of irritability of nerve cells, (c) regulation of coagulation of blood and of milk, and (d) regulation of normal heart action.

Phosphorus (1) furnishes an important component in the formation of bone salts and of muscle and nerve tissue; (2) plays a role (a) in absorption of carbohydrates and their transformation in muscular activity, (b) in transportation of fatty acids and probably in absorption of fat, and (c) as a buffer, in maintenance of acid-base equilibrium; (3) as cephalin, is essential for the formation of thrombin in coagulation of blood.

More than half the amount of calcium stored when the infant is born at term has been acquired, according to Smith (322, pp. 222– 227), during the last 8 weeks of gestation. "In general, the increase of phosphorus in the fetal body follows a curve like that for calcium, rising (though less steeply) during the last months of gestation." For the premature infant the limiting factor is this interrupted antenatal storage period and not any "essential inadequacy of the organism." This is borne out by the findings of Benjamin and her coworkers (33, p. 416), after study of the retention of calcium and phosphorus by six premature infants, that "the infants retained a greater portion of the intake of both minerals than is reported for full-term infants" and that they retained more when they were given more.

The most important factors in the absorption of calcium into the blood, mostly from the small intestine, are given by Hansen (136, p. 66) as "the amount of calcium in the diet, the calcium-phosphorus ratio, and the presence of vitamin D..." Vitamin D, as well as a high degree of acidity in the intestinal tract, increases the absorption of phosphorus, according to Hansen (p. 70), which is hindered, on the other hand, by excessive amounts of calcium and fat in the diet.

During the rapid growth characteristic of early infancy the percentage of calcium in the body decreases sharply and that of phosphorus rises in all infants. Stearns (335, p. 418) has shown that in the premature infant whose diet is human milk only, the decrease in calcium is relatively greater than in the full-term infant who is on either human milk or cow's milk. "It is not surprising," Stearns comments, "that prematurely born infants who have been fed only human milk almost invariably develop rickets."

Cow's milk has a much higher calcium content than human milk (0.122 percent compared with 0.034 percent) and, in addition, the cow's milk calcium seems to be better utilized by premature infants. Benjamin and coworkers (33, p. 425) found by experimental feed-

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ing of three healthy premature infants on cow's milk and three on human milk, that the utilization of the calcium of cow's milk was greater than that of human milk, possibly because the smaller amount of phosphorus in human milk "acted as a limiting factor in the retention of calcium." Supplements of vitamin D, which all six of the infants were receiving, increased calcium retention. The authors found, however, that in the infants fed human milk retention of calcium was inadequate to meet the level that they calculated was the minimum acceptable; in all three of those fed on cow's milk the retention surpassed this lowest requirement, and in two of them it surpassed the amount that "would permit the premature infant to commence from birth systematically to correct his initial deficit and attain by the end of a year the degree of calcification shown by a full-term infant."

end of a year the degree of calcification shown by a full-term infant." "From the standpoint of skeletal formation," Benjamin and her coworkers comment (p. 424), "it may be concluded . . . that for premature infants human milk is not the food of choice unless it is supplemented with both calcium and phosphorus, as, for instance, by the addition of calcium paracaseinate." (For discussion of modification of human milk see p. 168.)

Iron

According to Holt and McIntosh (155, p. 160), "iron forms an integral part of the hemoglobin molecule and of the cytochromes, which are respiratory pigments found in all cells; it also serves as a catalyst to red-cell formation." The absorption of iron in the intestine is incomplete; it "is favorably influenced by an abundance of calcium and other metals which unite with phosphorus." Vitamin D also exerts an indirect influence on the absorption of iron. "Inorganic iron is more readily assimilated than food iron; it is also a more effective hematopoietic stimulant." For infants 6 to 8 months of age an iron intake of 6 mg. per day is recommended (242).

Considerable evidence has been accumulated that iron given in the neonatal period is not effective in preventing the so-called "anemia of prematurity" which occurs in the early weeks of life. Blackfan and Diamond (36, p. 25) report that "actual measurements of the iron concentration in the liver and other viscera of premature infants have failed to demonstrate a poverty in this element." Smith (322, p. 229 ff.) says that iron is added to the fetal body in amounts that depend to some extent on the maternal intake. He has also reviewed the medical literature and presents the following conclusions:

- 1. Studies of Pommerenke and his associates (265) with radioactive iron fed to pregnant women have shown that the iron reached the fetal circulation within 40 minutes after ingestion.
- 2. Studies of Toverud (355) and of Iob and Swanson (167) have shown that the fetal liver contains more iron as gestation proceeds; but according to Iob and Swanson, this is an apparent, rather than an actual, increase, being related, as Smith says, "in some part to the physiological removal of water from the body during this period."
- 3. At birth the blood has been shown to have an amount of hemoglobin beyond the requirements of its new environment. A fall in hemoglobin and red-blood cells occurs in the early weeks of life which is considered physiologic.

In premature infants these changes are more marked and last longer. There has been no general acceptance of the idea that this anemia can be prevented by giving iron. "Once it is well established the period of 'physiological anemia' may indeed be curtailed by the feeding of extra iron, and the more true anemia of prematurity may, by the same measure, be made less severe and more like that following full-term birth."

Whether or not administration of iron makes the early anemia less severe, it seems to be agreed that it serves as prophylaxis against the later development of iron-deficiency anemia. For this purpose administration may be begun at 6 weeks of age and should not be delayed beyond the age of 3 months. Blackfan and Diamond (36) say that recovery from the early anemia is spontaneous and should have occurred by about the seventh month unless interfered with by nutritional disturbances, infections, or congenital anomalies, but that an iron preparation after the third month may be of value. Pierce (259) agrees that iron is without effect in preventing the early anemia and that spontaneous recovery is to be expected in full-term infants. However, in view of the fact that in premature infants physiologic anemia sometimes manifests itself in exaggerated form, while their rapid rate of growth makes their demand for iron greater than that of full-term infants, she advises the medicinal use of ferrous sulfate after the third month as prophylaxis against the development of a true iron-deficiency anemia. (For causes and treatment of anemia in premature infants see p. 297.)

VITAMIN REQUIREMENTS

The premature infant's needs for certain vitamins are greater than the full-term infant's for the following reasons:

- 1. Antenatal storage of vitamins is incomplete.
- 2. The rate of growth is greater in the premature infant than in the full-term infant.
- The amount of milk taken is small and its content of some vitamins is lowered by boiling.
 The recommended low-fat milk contains less vitamin A,
- 4. The recommended low-fat milk contains less vitamin A, and defective fat absorption interferes with the absorption of fat-soluble vitamins A and D if the infant is fed whole cow's milk or human milk.
- 5. Diarrhea, to which there is a tendency, may increase vitamin loss, particularly of the vitamin-B complex and vitamin C.
- 6. Infection, to which premature infants are highly susceptible, may increase the vitamin requirements.
- The premature infant needs larger amounts of vitamins A, C, and D than does the full-term infant, and 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 are desirable. To the question what amounts of the vitamins should be given to protect the premature infant and provide for optimum growth on the one hand, and to cure him of deficiency diseases on the other, research has as yet supplied only a partial answer; for the full-term infant recommendations as to both

preventive and curative requirements (except for the vitamin-B complex) have been made much more definite.

Incomplete as is the definite information with regard to the vitamin needs of premature infants, it is recognized that prophylactic administration of vitamins is especially important for these infants. It may be that slight vitamin deficiencies affect the nutrition of the premature infant in ways not now demonstrable and that in these infants even serious deficiencies can exist without the clinical signs and symptoms manifested in more mature infants and in older children.

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 full-term infant, who takes large amounts of milk compared with the premature infant. Thiamine is not supplied in high concentration in milk, and the amounts of vitamins C and D in milk are inadequate even for the full-term infant.

The prophylactic administration of vitamins is discussed in connection with feeding. (See p. 176.)

Vitamin A

Function and sources

"Vitamin A has two specific purposes in the diet. First, it supplies a complex which unites with protein to form rhodopsin (visual purple), a substance in the rods of the retina concerned with accommodation to light, and iodopsin (visual violet), a substance in the retinal cones also concerned with vision. Secondly, it supplies a factor which affects the metabolism, development, and maturation of epithelial cells (136, p. 79)." Most of the supply of vitamin A is stored in the liver. Carotene is converted into vitamin A in the body; where and how the conversion takes place are not known. (See 314.)

The normal newborn infant, according to Lund and Kimble (212, p. 216), has a smaller supply of vitamin A both in the liver and in the blood than does the mother, and the cord blood contains only traces of carotene. They found the plasma vitamin A of the newborn infant to be independent of the maternal plasma vitamin A, and they agree with Byrn and Eastman (58) that administering large amounts of vitamin A to the mother shortly before delivery does not raise the vitamin-A value of the infant's cord blood. How the vitamin is transferred from the mother to the fetus is not definitely known.

After birth a marked drop in the supply of plasma vitamin A in the first 48 hours and a rise to a normal level on the fourth day was a physiologic phenomenon found by Lewis and his coworkers (207) in observations on 108 normal full-term infants and attributed by them to delay in the release of vitamin A from the liver and other organs and also to the infant's low intake of the vitamin in the first days of life.

In regard to observations on premature infants, Lund and Kimble (213) found especially low values of vitamin A in the cord blood of the 5 premature infants included in their series, and this finding led them to test the relation of birth weight to the supply of vitamin A. They found the average vitamin-A value in the cord blood of the 71 infants weighing less than 7.4 pounds (average 6.4 lb.) to be lower than the average for the 76 infants weighing more than 7.4 pounds (average 8.3 lb.). The authors conclude: "Thus it would seem that

low vitamin-A values are related to a low birth weight or possibly to some element associated with low birth weights."

In regard to postmortem determination of the vitamin-A content of the liver, Toverud and Ender (356) found it generally higher in 47 premature infants than in 50 full-term infants; but after studying maternal diet in relation to the infants' vitamin-A supply, they concluded that that supply was more dependent on the mother's diet than on the infant's maturity. Results of postmortem examination of the livers of 16 premature and 7 full-term infants indicated to Henley and associates (145), however, that "the maturation process plays a role in vitamin-A storage as it does of iron, calcium, and so forth."

Prevention of deficiency

A number of studies have been made of the blood vitamin-A level during the neonatal period. Henley and associates (145) made comparative tests of (1) absorption of vitamin A by 10 premature in-fants (11-60 days old) and 10 full-term infants (6-70 days old), and (2) retention of dietary fat by 8 premature and 2 full-term infants. They also studied blood-plasma levels of vitamin A in 89 premature infants at 3 weeks of age, 51 of whom had received supplementary vitamin A from the third day of life. Their results suggest that "both age and prematurity influence efficiency of absorption of vitamin A" and that there is a "direct parallelism" between absorption of fat and absorption of vitamin A. The blood-plasma levels were not significantly different for the 44 infants who weighed less than 2,000 gm. at birth and the 45 infants who weighed 2,000 gm. or more; but the levels were significantly higher in the infants who received supplementary vitamin A, and about one-fourth of those who had not received the supplement had levels below the "acceptable minimum.". Henley and associates concluded: "Because premature infants have relatively low reserves of vitamin A in the liver, because they are likely to absorb both dietary fat and vitamin A less efficiently than full-term babies, and because many premature infants not receiving supplements of vitamin A have low levels in the blood plasma, deficiency of this vitamin may be expected to develop earlier in these infants. These results suggest that early supplementation of premature in-fants' diets with concentrates containing vitamin A is a desirable routine procedure."

Henley and associates (145) also call attention to the fact, already mentioned in connection with all vitamin deficiencies in premature infants, that the handicaps from which these infants suffer "rarely result in clinical signs of vitamin-A deficiency, but they indicate that subclinical deficiency may develop quickly if the diet is not supplemented with vitamin A."

The blood-plasma level of vitamin A, on which Henley and his coworkers based these conclusions, in part, is regarded by May and his coworkers (221, p. 1184) as a "useful direct clinical test for early diagnosis of deficiency of vitamin A" before reliable clinical signs appear. (For prophylactic administration of vitamin A see p. 176.)

Deficiency

Vitamin-A deficiency may develop, according to Holt and McIntosh (155, pp. 135, 254, 255), "(1) because of inadequate intake, (2) in conditions of impaired intestinal absorption, and (3) in certain dis-

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orders which affect its utilization. . . It is seldom noted [in premature infants] except in infants who have been fed low-fat formulas." They observe that several of the cases of vitamin-A deficiency seen in Baltimore "were in very young infants, some of them premature, who had been fed on low-fat formulas without supplements of vitamin A." They mention congenital atresia of the bile ducts (see p. 204), dysentery, the celiac syndrome, and severe infections as conditions that predispose to vitamin-A deficiency. (For relation of experimental vitamin-A deficiency in rats to the occurrence of congenital malformations in the offspring see p. 187.)

Vitamin-A deficiency in a premature infant has been reported by May and associates (221) who studied the blood levels of vitamin A and of carotene in a 1-month-old premature infant weighing 434 lb. at birth and 414 lb. at 1 month. The infant had been fed on his mother's milk plus a "grossly inadequate formula." He was found to have severe edema, a low serum protein, and a very low vitamin-A level, though there was no clinical evidence of vitamin-A deficiency. He was given fat-free milk to limit his intake of vitamin A to the concentrated form of carotene in oil, which was given in large quantities. (Carotene has half, or less than half, the value of vitamin A.) The levels of carotene and vitamin A in the blood rose to high values after 11 days.

Treatment

The therapeutic dose of vitamin A for premature infants has not been established. Without mention of prematurity, Holt and Mc-Intosh (155, p. 259) say that in treatment of vitamin-A deficiency "10 drops of halibut-liver oil or percomorph-liver oil three times a day providing 50,000 to 60,000 international units should be adequate for any case unless there is absorption difficulty" and "satisfactory results can in most instances be obtained with smaller doses" (approximately 18,000 units). McCreary and Tisdall (223, p. 9) also suggest 10,000 to 20,000 units for treatment of vitamin-A deficiency and 50,000 to 60,000 units "if there is any defect in fat absorption."

Vitamin-B complex

The vitamin-B complex is made up of closely associated watersoluble substances, of which about 20 have been described, according to Hansen (136, p. 81). Some he classifies as essential for the nutrition of children, some as probably essential, and others as playing a role in human nutrition that is not yet determined. They are generally described under the name "vitamin-B complex" because they tend to occur together. Moreover, those whose functions are best known (thiamine, riboflavin, and niacin) are so interrelated that a deficiency of one appears to interfere with the functioning of the others. For this reason and because this interrelationship may also apply both to the "probably essential" group (pyridoxine, pantothenic acid, biotin, choline, inositol, and para-aminobenzoic acid) and to those components whose functions, if any, in human nutrition are not yet defined, preparations containing the vitamin-B complex are advocated for prevention or treatment of deficiency in any of the components. The B-complex vitamins and the amino-acids are also interrelated, according to Ruskin (301), neither being utilized without the other. Folic acid, one of a number of related, if not identical, factors (lactobacillus case factor, vitamin Bc, vitamin M)—a component of the vitamin-B complex in the group whose relation to human nutrition was classified as undetermined—has been the subject of considerable recent research in relation to anemia. It is reported by Zuelzer (414) and others to be ineffective in the early anemia of premature infants.

Yeast in tablets, powder, or liquid form, contains all the components of the vitamin-B complex. Where there is known to be a deficiency of one of the components it may be necessary to supplement the vitamin-B complex with the specific component indicated.

Thiamine, riboflavin, and niacin are widely distributed in foodstuffs. Each contributes to the functioning of enzyme systems concerned with cellular respiration and with carbohydrate and fat metabolism. Only these components will be discussed separately.

There is growing evidence that, like the vitamins about which more is known, the dietary supply of the vitamin-B complex needs to be supplemented for the premature infant, though the amount that should be given has not been established. Anderson (25) comments that for the premature infant "there is no harm in prescribing average infantile requirements as a preventive measure." Moreover, Litchfield and his coworkers (211) call attention to the fact that according to a number of investigators, the vitamin-B complex, especially the antineuritic B_1 factor, "may be present in too low concentration in cow's milk, as well as in human milk, for the optimal well-being of the infant. In the process of sterilization the B_1 factor may be further decreased, for it has been shown to be heat-labile . . ." These authors made a study of 58 premature infants born in 1 year in two Brooklyn hospitals; all received from birth varying amounts of yeast extract. The infants given yeast extract began to gain weight much sooner and gained much faster than the premature infants born in a previous year, who had not received it, and the yeast extract caused no gastrointestinal disturbances.

Absorption of the vitamin-B complex from the intestines is interfered with by vomiting, diarrhea, or any other gastrointestinal disturbance or abnormality. (For prophylactic administration of the vitamin-B complex see p. 176.)

Thiamine (vitamin B_1)

Function and sources

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Thiamine (vitamin B_1) "plays an important role," according to Holt and McIntosh (155, p. 262), "in the intermediary metabolism of carbohydrate; thiamine phosphate (cocarboxylase) is the functional part of an enzyme which assists in the oxidation of pyruvic acid. In the absence of thiamine sugar cannot be completely burned, and pyruvic acid accumulates in the blood and tissues. The conversion of sugar into fat is likewise interfered with. The body as a whole suffers in thiamine deficiency, but the clinical effects are most conspicuous in the nervous system and, next to this, the heart."

The store of thiamine in the body is more limited, according to Holt and McIntosh, than that of any other vitamin, and deficiency may develop within 2 or 3 weeks if the intake or the absorption is inadequate. . •

Prevention of deficiency

Thiamine does not occur in high concentration in milk, though there is more in cow's milk than in human milk. Moreover, both cow's milk and human milk for feeding young premature infants must be boiled, and boiling destroys a considerable percentage of the thiamine. Studies of the adequacy of thiamine in milk for infant feeding have been made by Knott (183) and by Clements (65). A diet high in carbohydrate and low in fat, like that of the premature infant, may call for supplementary thiamine (289 and 123).

Deficiency

No cases of proved deficiency of thiamine in premature infants have been found. Van Gelder and Darby (365), however, have reported a case of severe thiamine deficiency in the newborn infant of a mother who showed slight edema and was on an inadequate diet during pregnancy, and after a later test on this diet proved to have a very low level of thiamine in the urine. The infant had cyanosis, tachycardia, and cardiac hypertrophy, together with feeding difficulties, which cleared up with thiamine therapy. The mother was considered to have had undiagnosed subclinical beriberi.

Treatment

Except for frank beriberi, which develops with extreme deficiency, the therapeutic dose of thiamine for infants has not been established. Hess and Lundeen (143, p. 148) say that "in the presence of anorexia, diarrheal conditions, increased elevation of metabolic rate seen in acute illness in the premature infant, the daily addition of 1 mg. (333 I. U.) or more of thiamine hydrochloride can be administered with beneficial effect. If there is doubt as to its complete absorption the thiamine hydrochloride can be injected hypodermically." According to Hansen (136, p. 83), no harmful effects have been reported even from the use of "enormous quantities of the synthesized product."

Riboflavin

Function and sources

The function of riboflavin has been thus stated by Hansen (136): "In the body riboflavin forms a part of a respiratory enzyme system by combining with phosphoric acid and a protein. . . It is also said to play a part in the metabolism of iodopsin [a substance in the cones of the retina]." According to Bicknell and Prescott (34, p. 315)"riboflavin enzymes or flavoproteins form part of the system for the metabolism of carbohydrate" and "riboflavin appears to play an important part in the nutrition of the eye." It "can only exert its proper metabolic function when B₁ is also present (64)." Riboflavin is stored in the liver, heart, and kidneys, and may possibly be synthesized in the intestines.

Prevention of deficiency

Milk is a rich source for this vitamin, and cow's milk contains about five times as much as human milk. But the small amount of milk taken by a premature infant, especially one who is very small or feeble, cannot be counted on as the sole source of supply. There is little destruction of riboflavin from heat, but it is extremely labile when exposed to light.

Deficiency

Riboflavin deficiency is said to be rather common in children, especially in connection with deficiencies in other components of the vitamin-B complex. Little is known, however, about its occurrence in premature infants. Stevenson (336) reported a case of possible ariboflavinosis in a premature infant weighing 1,990 gm. at birth whose symptoms (lesions around the mouth) appeared on the thirteenth day of life but disappeared when 3.0 mg. of riboflavin were administered by mouth daily for 3 days. The author pointed out that the need of the premature infant for riboflavin probably is relatively great—too great to be met from milk alone. "There is very little storage of riboflavin in the body and a deficiency might quickly become evident."

(For discussion of congenital malformation in rats resulting from experimental deficiency of riboflavin in their diet see p. 187.)

Treatment

The therapeutic dose for premature infants has not been established. For children Warkany (378) suggests 3 to 10 mg. daily by mouth and if this is not effective within a few days, 2 mg. intramuscularly in saline solution three times daily. "In addition to the treatment with riboflavin, the children should be given . . ., temporarily at least, more than the usual requirements of the B complex." According to Hansen (136, p. 82), large doses do not cause toxic effects.

Niacin (nicotinic acid)

Function and sources

Niacinamide, the physiologically active form of niacin, according to Holt and McIntosh (155, p. 153), "has been shown to be the functional group of several coenzymes concerned with the oxidation and synthesis of carbohydrates and amino-acids." Bicknell and Prescott (34, p. 388) say that niacin "is present in practically all tissues; the liver contains more than any other organ . . . A period of months is required to deplete the body of sufficient of its stores of nicotinic acid to produce pellagra."

Prevention of deficiency

Milk seems to be more effective in preventing niacin deficiency than would be expected from its relatively small content of the vitamin. Loss from boiling the milk and from exposure to light is small. However, from the evidence available it would appear that premature infants need supplements of this vitamin because of the small quantity of milk that they are able to take.

Deficiency

No reports of deficiency of niacin in premature infants have been found.

Treatment

If niacin deficiency is suspected because of the mother's condition it may be advisable to give niacinamide as well as the vitamin-B complex. The therapeutic dose has not been established, but only slight and temporary unfavorable effects have been found from the use of niacin and none from the use of niacinamide (136). (In infants suffering from severe pellagra, involving damage to the liver, some unfavorable results have been reported from vitamin-B therapy. See 113.)

Ascorbic acid (vitamin C)

Function and sources

Ascorbic acid is the chemical name for vitamin C which has long been known as the antiscorbutic vitamin. More recently it has been found to fulfill other functions, though little is known as to the way in which it operates. It is necessary for the formation of intercellular substance "in which tissue cells are embedded and cemented together (136)." (See vitamin P, p. 167.) Ascorbic acid is also necessary for the formation of bone and cartilage. It has been found by Levine and his associates (206) to be involved in the metabolism of aromatic amino-acids, and it may be involved in carbohydrate metabolism.

The level of ascorbic acid in the blood of the newborn infant is higher than the maternal level because the fetus not only depends on the mother for vitamin C but abstracts it at her expense. Lund and Kimble (213) found that about 80 percent of the 94 newborn infants studied had a "normal complement" of vitamin C. However, 25 premature infants examined postmorten by Toverud (354) at or shortly after birth were found to have a lower supply of vitamin C in the liver than 31 full-term infants under similar conditions of maternal diet. There is a rapid fall after birth unless the vitamin is supplied in the diet, as this vitamin is not synthesized in the body.

Ascorbic acid is found in practically all the tissues and body fluids. According to Bicknell and Prescott (34, p. 499), "it appears that vitamin C is stored in those organs and tissues with a high metabolic activity and is present to a greater extent in the tissues of the young."

Prevention of deficiency

The amount of ascorbic acid in human milk is much greater than in cow's milk; but, as the amount of human milk varies greatly with the mother's diet, supplementary ascorbic acid, usually in the form of orange juice, is recommended even for full-term infants, whether breast-fed or bottle-fed. For premature infants supplementary ascorbic acid which, at least, in the early days of life, should be administered in synthetic form, is especially important because the amount of milk taken is small, and both cow's milk and human milk must be boiled. Both boiling and exposure to light destroy some of the vitamin C. Moreover, a high-protein diet, such as is needed by the premature infant (see p. 146), has been shown by Dann (74) to call for an increased amount of ascorbic acid. Infections may interfere with the absorption of the vitamin in the intestines and thus increase the amount required. (For prophylactic administration of ascorbic acid see p. 177.)

Deficiency

Clinical evidences of scurvy are rarely found in infants under 5 months of age, but subclinical deficiency of ascorbic acid will occur much earlier if body stores are depleted because of inadequate intake. Histologic evidence of earlier occurrence of scurvy in which clinical evidence had not been observed has also been reported. Ingalls (162) found postmortem evidence of scurvy in three premature infants

who were fed pooled pasteurized human milk without added vitamin C and who died at the ages of 26, 32, and 57 days, respectively.

Treatment

In the presence of symptoms or signs of scurvy ascorbic acid should be given in large doses. The oral dose recommended for infants by Warkany (379) is 100 mg. or more daily. Goettsch (114) has shown that "a single massive dose [400 mg.] of cevitamic acid [ascorbic acid] . . . appears to favor healing of infantile scurvy as effectively as would the same total dose given in small daily portions over a period of 8 days." Healing occurred more quickly, and "no untoward reaction" followed the massive doses. For treatment of scurvy in premature infants ascorbic acid should be given intravenously in a solution especially prepared for the purpose (the sodium salt of ascorbic acid in a sterile, buffered physiologic solution, prepared just before it is administered). In some cases of scurvy that did not respond to ascorbic acid vitamin P has been found effective.

Vitamin-C therapy has also been found effective in combating a defect in protein metabolism reported by Levine and associates (206; see also 205, 74, 203). At ages varying from 13 to 47 days five premature infants on diets of powdered milk adequate for their needs in other respects but lacking added vitamin-B complex and ascorbic acid were found to have a defect in the metabolism of aromatic amino-acids, which the authors related to the higher content of those amino-acids in cow's milk. Thiamine therapy was ineffective, but the abnormal products disappeared from the urine promptly when totals of 150 to 525 mg. of ascorbic acid were given, orally or parenterally.

Vitamin D (antirachitic vitamin)

Function and sources

Vitamin D, according to Eliot and Park (97, p. 54), promotes calcium and phosphorus absorption from the 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.

Provitamin D is present in the skin and is activated by the ultraviolet rays of the sun. The principal forms of vitamin D are described by Hansen (136, p. 77) as follows: "Activated ergosterol (vitamin D_2 , viosterol, calciferol) from vegetable sources and irradiated 7-dehydrocholesterol (vitamin D_3), a naturally occurring vitamin from animal sources, are probably the most important of the 10 or so sterols which have been found to possess vitamin-D activity. . . . The vitamin D formed in the skin is absorbed directly into the blood stream. . . . Vitamin D is fat-soluble and when ingested is absorbed . with fat from the intestine. . . The metabolism and mode of action of [these substances] are not well understood, but these appear to be concerned with the absorption of phosphate from the intestinal tract."

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 in pregnancy. Toverud and Ender (356) found by indirect measurement no vitamin D in the livers of 24 out of 44 newborn infants examined postmortem, small amounts in 15, and larger amounts in 5. Some of these infants were premature, but the authors found no correlation between the amount of vitamin D and fetal age. The mothers of the 5 infants with the largest storage of vitamin D had had unusually large amounts of milk and eggs in their antenatal diets and one of them had also had cod-liver oil.

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, as is shown by the length of time that massive dosage (see p. 163 ff) is effective.

Prevention of deficiency

Deficiency of vitamin D is manifested by rickets alone or associated with tetany. (See pp. 323, 330.) Rickets "appears in most premature infants unless special preventive measures are taken and often in spite of them (97, p. 8)." The need for beginning administration of vitamin D earlier for premature infants than for those born at term is emphasized by the fact that in premature infants "rickets develops earlier, progresses more rapidly, and tends to be more severe . . ." Reasons given by Eliot and Park (97, p. 9) for the peculiar susceptibility of premature infants to rickets are intensity of growth, together with low calcium reserves at birth, inefficient utilization of calcium and phosphorus, and inefficient utilization of fat, which may involve inefficient utilization of fat-soluble vitamin D. Moreover, premature infants do not get the benefit of direct sunlight for a considerable period and they are highly susceptible to infection and to diarrhea.

Vitamin D is present in small amounts in both human milk and cow's milk, but large amounts of supplementary vitamin D are required for the premature infant.

The minimum daily requirement of vitamin D for the premature infant is believed to be greater than that for the full-term infant but has not been definitely established. Jeans and Stearns (172), on the basis of balance studies and review of published material, tentatively set the daily requirement for the full-term infant at 300 to 400 international units and of the premature infant at approximately twice this amount during the early period of most rapid growth. Jeans and Marriott (171, p. 391) have more recently stated their belief that 800 units is fully adequate for protection of the premature infant. Eliot and Park (97, p. 104), on the other hand, on the basis of clinical and pathologic studies, state that "to premature infants it may be necessary to give 1,000 international units or even more daily . . ." Park (252) states that for the premature infant the required dosage may be 5,000 to 10,000 units or even more daily because he is especially susceptible to rickets. For this reason Davison (78, sec. 242) recommends beginning with administration of about 3,600 international units, to be increased 5 days later, if the smaller dosage is tolerated, to 5,400 units.

Malmberg (219), after a study of 22 premature infants ranging in birth weight from 1,150 to 2,000 gm., concluded that premature infants weighing 2,000 gm. or less need about 10,000 international units of vitamin D_s daily, or at least more than 6,000 international units, from the second half of the first week of life, if they are to escape rickets. In a later study of 72 premature infants receiving varying daily amounts of vitamin D, Malmberg (220) concludes that 2,700 to 5,400 units is inadequate to protect premature infants against rickets, whereas 10,000 units daily or a massive dose of 500,000 units

will give adequate protection, even to those in the lower weight groups. (See Rickets, p. 324.)

Sydow (344, pp. 18, 50) made a comprehensive chemical and roentgenographic study of the development of rickets in a series of 118 premature infants weighing 1,010 to 2,000 gm. "who were considered able to be subjected to the necessary examinations without risk." Different groups received human milk and cow's milk with and without supplements of vitamin D. Statistical analysis of the results of vitamin-D administration on the blood was based on the infants who had had at least 25 daily doses of 5,000 to 10,000 international units or had had a massive dose of 500,000 units at least 25 days before the first chemical determinations. Roentgenograms were started earlier.

The author found (pp. 66, 56) the most favorable results in the group of infants given cow's milk plus vitamin D. Very few of these infants showed roentgenographic signs of rickets. Their serum-calcium level was a little below normal and was about the same as that of the group given human milk plus vitamin D, but their serum inorganic-phosphorus and phosphatase levels were normal, whereas those of the group given human milk plus vitamin D were abnormally low for phosphorus and abnormally high for phosphatase and were not significantly different from those of the group given human milk without vitamin D. The author comments (p. 109): "Neither a supply of vitamin D nor of cow's milk is certain to prevent rickets. . . . Even where rickets is not prevented there is generally an effect of the supply on the serum values; i. e., vitamin D has increased the serum calcium and cow's milk has increased the serum inorganic phosphorus and decreased the serum phosphatase, even in the cases where rickets has developed." (See also Rickets, p. 327.)

Reports of the use of massive doses of vitamin D for the prophylaxis of rickets have appeared in the medical literature in considerable numbers in the past decade. Reports of this type of prophylaxis for premature infants are few in number, however. Zelson (413) reviewed the literature and reported his findings on the single-dose treatment of 46 premature infants between 12 and 33 days of age, of whom 26 received by mouth 200,000 to 500,000 international units of electrically activated ergosterol and 20 received 600,000 units of D_2 and D_3 parenterally. Observations for evidence of rickets were reported for only 17 of these infants, the periods covered varying from 13 to 254 days. Evidence of rickets was found in only 1 infant. "None of the 46 premature infants showed any clinical signs of toxicity or calciumcontaining casts in the urine. . . ."

Wolf (401, pp. 400, 403, 408) reported a study from September 1941 to June 1942 of 75 infants given 600,000 international units of electrically activated ergosterol in cereal, divided into 2 doses at 24-hour intervals, at about the third to the fifth month of life; a second 600,000units was given to some of the infants from 3 to 6 months later. Sixtytwo of the infants were observed for 2 to 7 months. At the time the first massive dose was administered 18 of these infants (2 weighing only 5 lb. at birth) showed roentgenographic evidence of mild rickets, 25 (2 premature) showed no roentgenographic evidence of rickets, and 19 were not examined roentgenographically. The follow-up report showed healing and no recurrence in the 18 mild cases and no evidence of rickets in the 44 other cases during the periods of observation.

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The same author (402) reported continued study from September 1942 to June 1943 of massive-dose prophylaxis in a series of 50 infants. This was a study of the results of administering to these infants 50,000 international units of concentrated vitamin D at 1 month of age, 50,000 units at 2 months, and 600,000 units at 3 months. For the younger infants (1 and 2 months) the vitamin was given in corn oil, which was added to one of the milk feedings; the later dose was given in cereal. Parenteral administration, Wolf (401, p. 416) believes, is necessary "only in cases of severe intestinal disturbances or in the case of young premature infants whose absorption may be poor." Because of war conditions follow-up was possible for only 21 of the 50 infants. Two of the 21 infants showed slight rickets after the second dose of 50,000 units; but this had disappeared when roentgenograms were taken 4 months after the 600,000-unit dose was given. The other 19 infants, followed for 4 to 9 months, showed no evidence of rickets.

No toxic manifestations occurred in either series of infants studied by Wolf. He considers (p. 416) that "there is no danger in administering single massive doses of vitamin D to young infants, even premature infants" but that the method of administration used in his second study "precludes even the slightest possibility of vitamin-D overdosage (p. 175)." The vitamin must be given in a pure form.

Excessively large amounts of concentrated vitamin D, on the other hand, from large and frequently repeated doses aggregating as much as 3,000,000 units may result, according to Wolf, in metastatic calcification of the tissues. He cites the case of an infant (401) with such severe congenital malformations that the outlook was hopeless, who was given tremendous doses of vitamin D to determine the toxic level. "Metastatic calcification of the kidney tubules was produced experimentally in an infant aged 3 months weighing $7\frac{1}{2}$ lb. at a level of about 85,000 U. S. P. [international] units of vitamin D per kg. given daily for 12 consecutive days"—a total of 3,500,000 units or more.

Rambar and his coworkers (282) followed 12 infants (none of them premature) who were given massive doses of vitamin D between October 1941 and April 1942. Eight of them received 600,000 international units in a single day; 4 received 100,000 units once a month for 6 months. On the basis of monthly clinical examinations, tests of blood calcium and phosphorus levels, and roentgenograms of the long bones, the authors concluded that massive oral doses given in a single dose of 600,000 units or in repeated monthly doses of 100,000 units per month are effective in preventing rickets. "No toxic clinical or laboratory findings occurred in any of the infants receiving this type of prophylaxis."

Two reports have come from Sweden dealing with the use of massive-dose prophylaxis against rickets in premature infants, in one of which the treatment was begun immediately after birth. Klackenberg (182, p. 513) gave 500,000 international units of concentrated vitamin D to 100 premature infants varying in birth weight from 1,250 to 2,500 gm. The dose was given by mouth—half at birth or on admission to the hospital and the other half a week later; only 2 infants received vitamin D in any form for 3 months afterward. The infants were reexamined clinically and roentgenographically 3 to 34 months after the massive dose was given. In 19 infants there were clinical evidences of rickets, but in only 9 were roentgenographic

evidences found. There were reported to be "no definite indications" of toxicity.

Johnsson (173, p. 476) reported a follow-up study of 71 premature infants (birth weight, less than 2,500 gm.) thus treated. In this series 250,000 international units of concentrated vitamin D_2 were given: later the amount was increased to 500,000 to 600,000 international units of D_3 , dissolved in 1 to 2 grains of peanut oil. At first the vitamin was administered by mouth; but as it sometimes caused vomiting, it was later injected intramuscularly. The vitamin was not given until the infant attained a weight of 2,000 gm.; or, if the birth weight was 2,000 gm. or more, the vitamin was given in a fortnight. During the observation periods of 3 months to 1 year, half of the infants had regular clinical and roentgenographic examinations for evidences of rickets, together with regular tests for the blood levels of calcium and phosphorus. The other half received "for the most part" only clinical examinations. Of the 36 infants examined roentgenographically 7, varying in birth weight from 1,400 to 2,130 gm., were found to have developed slight rickets in the latter half of the first 6 months; 6 of the 7 had received 500,000 to 600,000 international units of vitamin D.

No evidences of damage to kidneys or heart were demonstrated by urine examination (39 infants) or by electrocardiogram (40 infants).

Johnsson concluded (p. 483) from his own study and earlier studies that "premature infants are relatively well protected against rickets" by the massive-dose method, but that the prophylactic use of massive doses for premature infants should be "subjected to continued clinical testing." Apparently the amount of such testing that has been possible since Johnsson's report was written is deemed sufficient, for Lichtenstein, the head of the pediatric clinic on whose cases Johnsson's report was based, says that massive-dose prophylaxis for premature infants is now routine in the clinic. (Personal communication from A. Lichtenstein, M. D., Kronprinsessan Lovisa Children's Hospital, Stockholm, August 1946.) (For prophylactic administration of vitamin D see p. 178.)

Deficiency

Rickets in the premature infant is usually not diagnosed clinically until after the first month of life, although prenatal rickets has been reported.

Treatment

For the diagnosis and treatment of rickets in premature infants see page 323. See also Tetany, page 330.

Vitamin K

Function and sources

Vitamin K, Hansen (136, p. 80) states, "plays an essential part in prothrombin formation and thus in proper blood coagulation." It is fat-soluble as it occurs naturally "and apparently is absorbed readily from the upper part of the jejunum. Lack of bile in the intestinal tract predisposes to the development of a deficiency of vitamin K. It is not stored in the body to any extent, but what little is stored is probably in the liver. The action of vitamin K appears to be concerned with the integrity of the hepatic parenchyma, since the formation of prothrombin fails if the liver is badly diseased.... There is

considerable evidence . . . that this vitamin may be synthesized in the gastrointestinal tract, probably by bacterial action."

Vitamin K_1 has been isolated from alfalfa and vitamin K_2 from putrefied fish meal. Preparations of pure vitamin K_1 and K_2 are available in water-insoluble viscous oil and several preparations of synthetic vitamin-K analogues, the best known of which is menadione (K_4) , are available in oil- and water-soluble form. Fat-soluble preparations are usually given by mouth with bile salts, if there is biliary or intestinal obstruction, but this is not necessary with the watersoluble analogues, which may be given parenterally.

Prevention of deficiency

No method is known at present for measuring directly the concentration of vitamin K in the blood. The adequacy of vitamin K can be measured indirectly, however, in terms of blood-clotting time or prothrombin content expressed as the "plasma prothrombin level," "percent of normal adult value," or "prothrombin index."

The fetus in utero is supplied with vitamin K through the placental blood. After birth the prothrombin value decreases (the blood-clotting time increases) up to the third or fourth day, when the value increases (the blood-clotting time decreases), reaching a normal level by the seventh to the tenth day. Smith (322, p. 119) states: "As yet it has not been ascertained whether premature infants become more deficient in prothrombin than do those born at full gestation," and investigators that he cites come to different conclusions as to whether or not they show wider fluctuations than full-term infants in prothrombin time after the first day. Merritt and Davidson (230, p. 295) found the clotting time at birth for the great majority of a group of 73 normal, full-term infants to be 2 to 4 minutes and that of the majority of a group of 59 premature infants to be $1\frac{1}{2}$ to $4\frac{1}{2}$ minutes. These authors noted "more variation in the coagulation time of the infants of low weight at birth" compared with full-term infants. (For discussion of prothrombin levels see Hemorrhagic Disease, p. 292.)

Prophylactic administration of vitamin K to mothers before or during labor and to all newborn infants, including premature infants, is advocated—by one group for the purpose of preventing hemorrhage in the infant; by others for the purpose of preventing hypoprothrombinemia. Most authorities advocate the administration of vitamin K to premature infants because of their greater hemorrhagic tendency. Since the vitamin does no harm and may do good, it is probably best to give it to all premature infants immediately after birth, whether or not their mothers have received it. (For prophylactic administration of vitamin K see p. 178.)

Deficiency

Deficiency of vitamin K results in hypoprothrombinemia with or without hemorrhage. When the level of prothrombin falls below that considered physiologic, hemorrhage may but does not necessarily occur. Poncher (266) considers a level of 20 percent or less of the normal adult value as "usually critical." Some authorities believe that the hemorrhagic diathesis of the newborn, so-called "hemorrhagic disease," is thus explained; others consider the occurrence of hemorrage and the prothrombin level not necessarily related.

Treatment

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The therapeutic value of vitamin K has been well established in conditions associated with low plasma prothrombin levels. In hemorrhagic disease of the newborn the prothrombin level has not been found consistently low. It is stated that both the hypoprothrombinemia and the bleeding are effectively controlled by vitamin K in 2 to 6 hours (268). It is recommended that blood transfusions be given also when there is manifest hemorrhage. (For the therapeutic dose of vitamin K in cases of hemorrhage see Hemorrhagic Disease, p. 295.)

Vitamin P

Function and sources

Vitamin P, under this name or those of various substances related in structure (citrin, hesperidin, eriodictyol, rutin), is shown by clinical studies to be an "essential factor in human nutrition," according to Bicknell and Prescott (34, p. 859), who credit Scarborough's studies with having established this factor as essential for the maintenance of capillary resistance in human beings. It is called by Shanno (315) a regulating factor of vascular permeability. Its stores in the body and the way in which it operates are unknown.

Vitamin P occurs in many fruits, notably grapes, black currants, rose hips, and citrous fruits, and in the more recently available form, rutin, in tobacco leaves, buckwheat leaves and blossoms, and some 30 other plants. Scarborough (310) says that the sources "rich in ascorbic acid are not necessarily those with the highest vitamin-P potency."

Prevention of deficiency

No studies have been found in which vitamin P in any form has been used for prophylactic purposes. However, it should be noted that this vitamin is present in orange juice, so that infants who are able to take their vitamin C in this form get vitamin P also. The protective amount is unknown. It may be that premature infants, in whom the capillaries are fragile and who, at least in the first weeks of life, are taking synthetic ascorbic acid and not orange juice, would benefit from administration of rutin.

Deficiency

Scarborough (308) calls low capillary resistance, which is often but not always present in scurvy, an "expression of deficiency of vitamin P." The hemorrhages that develop from a deficiency of vitamin P, he says, "are always small and take place in the skin," whereas those "characteristic of deficiency of ascorbic acid are large and involve considerable areas of subcutaneous tissue and muscle." He mentions as clinical manifestations of vitamin-P deficiency "pain in the legs on exertion, shoulder pain, weakness, fatigue."

Treatment

Vitamin P has been reported to be effective in some cases of scurvy that did not respond to ascorbic acid (309) and in various other conditions that involved capillary fragility. The Journal of the American Medical Association (16), in response to an inquiry, says: "There is clinical evidence that administration of vitamin-P preparations favorably affects the lowered capillary resistance or spontaneous petechial hemorrhages associated with multiple vitamin deficiencies and found in certain diseases. Large doses of vitamin C promptly allevi-

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ate the gross hemorrhage manifestations of scurvy, but neither vitamin C nor vitamins A, B_1 , or D appear to raise the lowered capillary resistance which can be corrected by vitamin P." The Journal suggests an empirical dosage of 20 mg. of vitamin P twice daily.

The vitamin is reported to have shown no toxic effects.

Other vitamins

There are other vitamins which may be important to the welfare of premature infants but for which no data with regard to the needs of these infants are available.

Comparison of human milk and cow's milk

It has been shown that some of the peculiar needs of premature infants for various food elements can be met by a food with a high protein, low fat, and high calcium and phosphorus content. Table 46 shows the percentages of these constituents in human milk compared with cow's milk.

Cow's milk is much higher than human milk in protein, calcium, and phosphorus—constituents of special value for the premature infant. Human milk and cow's milk are equal in fat content, but cow's milk is more readily skimmed for fat reduction. The carbohydrate content of human milk is greater than that of cow's milk, but sugar added to cow's milk compensates for this difference and also for the calories lost in removing fat.

Human milk also may be so modified as to meet the premature infant's needs. The fat of human milk is difficult to remove by skimming and is not absorbed any better by the premature infant than is the fat of cow's milk. But Ylppö (408, p. 69) did remove a part of the fat from breast milk and reported satisfactory results in some premature infants receiving this human milk with 4 to 8 percent of sugar added. Kohl (185), on the other hand, found, in a study of 31 premature infants, that the addition of 2 percent gelatin to breast milk led to a definite gain in weight not obtained by adding 2 percent carbohydrate. For a small group of premature infants Langer (194) has reported that adding casein to human milk to supply the need for large amounts of protein during the first month of life resulted in greater gain in weight and fewer severe gastrointestinal disorders on a caloric intake lower than that of infants receiving breast milk alone.

	Percent of-							
Kind of milk	Protein	Fat	Carbo- hydrate (lactose)	Calcium	Phos- phorus	Other minerals	Water	
Human milk Cow's milk	1. 25 3. 50	3. 50 3. 50	7.50 4.75	0.034 .122	0.015 .090	0. 151 . 538	87. 55 87. 50	

TABLE 46 Percentage composition of cow's milk and human milk¹

¹Holt, L. E., Jr., and McIntosh, R. Holt's Diseases of Infancy and Childhood. 11th ed. D. Appleton-Century Co., New York, 1940. 1421 pp. (p. 194.)
Hess and Lundeen (148, p. 102) suggest that for infants weighing 1,250 to 2,400 gm. skimmed lactic-acid milk be added to human milk on the fourth or fifth day (or as soon as the infant is no longer having meconium stools) in order to increase the protein and mineral content, or that calcium caseinate be added for the same purpose.

Magnusson (217) reports the use of an amino-acid and human-milk mixture for feeding premature infants. Enzymatic hydrolysis of casein was brought about by the use of pancreatic ferments. The product was 80 to 85 percent free amino-acids, and the remainder was lower polypeptides. The solution-25 percent amino-acids, 25 percent glucose (added to supply calories), and 1.5 percent salts-was diluted with human milk or human milk mixed with water. From November 1943 to the time of writing such a mixture had been fed to about 150 premature infants, either continuously or intermittently, in addition to their regular diet, usually breast milk. The usual dose was 2.5 gm. of amino-acid per kg. of body weight plus an equal amount of glucose. The supplement was given to the very young infants by catheter, later by mouth. The author tabulates the weight gains of the infants receiving supplementary amino-acids during the first month in three birth-weight groups (1,301-1,400 gm., 1,601-1,700 gm., and 1,901-2,000 gm.), with comparative figures for infants receiving only breast milk during the periods indicated. He found that in all three weight groups the gains of the infants on amino-acids were twice as great in the first month as the gains of those on breast milk alone. That this difference was due in part to the amino-acids and not wholly to the higher caloric intake was the author's conclusion after testing some infants with an equal caloric supplement of unhydrolyzed casein with glucose and salts. These infants gained more than those on breast milk alone but less than those on the amino-acid mixture. The infants had no symptoms of digestive disturbances.

Whether the amino-acid supplement should be given to all premature infants or only to those who are not doing well on human milk alone and how long the amino-acid supplement should be continued, the author says, are unanswered questions. He notes, however, with reference to the second question that in a group of infants tested by him, the difference in weight gain became less marked after the second month.

In a study by Block and Bolling (41) in which they analyzed the amino-acid composition of the proteins of human milk and of cow's milk the authors concluded that human-milk proteins are not nutritionally superior to the proteins of cow's milk.

Gordon, Levine, and McNamara (121) studied the effect of 3 types of milk feeding on the rate of growth, in the period from 7 to 28 days after birth, of 122 healthy white premature infants weighing at birth 1,022 to 1,996 gm. All the infants were cared for under similar medical, nursing, and environmental conditions.

The analysis of the data was made according to sex, single or multiple birth, and birth weight. The first two factors were found not to be significant. When infants weighing at birth less than 1,621 gm. (the mean birth weight) were compared with infants weighing more than 1,621 gm. but less than 2,000 gm. significant differences were found in the rate of growth of infants fed pooled unmodified human milk (16 infants), evaporated whole milk with added carbohydrate (39 infants), and a powdered half-skimmed cow's milk mixture with added carbohydrate (67 infants) in amounts to provide 120 calories per kg. of body weight.

For the total group of 122 infants the mean daily gain in weight per kg. during the period of study was significantly larger for the groups of infants fed cow's milk mixtures (evaporated and halfskimmed milk mixtures) than for the group fed human milk. The mean daily gain was 12.5 gm. per kg. on human milk, 14.1 gm. on evaporated milk, and 15.7 gm. on half-skimmed milk. The smaller infants (less than 1,621 gm.) showed striking differences in rates of gain on the 3 feedings. The most rapid rate of gain (17.3 gm.) was in those fed the half-skimmed milk mixtures (31 infants); the slowest rate (11.7 gm.), in those fed human milk (4 infants). (A shortage of human milk while the study was in progress limited the number of infants tested with this type of feeding.) The differences were found to be not significant among the group of infants of higher birth weight (more than 1,621 gm.).

Fourteen infants weighing less than 1,000 gm. on admission to the hospital, who were not included in the statistical analysis, were fed daily 120 calories per kg. of the skimmed-milk mixture. The mean daily gain of 11 of these infants who were on this feeding from the seventh to the twenty-eighth day of life was 17.6 gm.

The authors conclude from this study that "under conditions of modern hospital practice," low-fat cow's milk will produce larger gains in weight than human milk in the feeding of premature infants, particularly the smaller infants (those weighing less than approximately 1,600 gm.).

The authors recognize the importance of the psychologic aspect of breast feeding; and since no significant difference was found in the rate of gain of the larger infants on human and on cow's milk feeding they suggest that larger premature infants should receive milk from their own mothers when it is easily obtainable, until they are able to nurse at the breast. The authors also comment on the findings in other studies (already referred to on pp. 168–169) that modifications of human milk have increased the infants' gain in weight.

Both human milk and cow's milk need to be modified if either is to meet to the fullest extent possible the known needs peculiar to the premature infant. Results of metabolic studies and their clinical applications have established certain principles with respect to the premature infant's requirements of protein, fat, and calcium, as well as his caloric and fluid requirements. As the infant becomes older and more mature the ability to store minerals and the tolerance for fat increase, and human milk then becomes as satisfactory as cow's milk mixtures. For this reason and for various psychological reasons, the mother's milk should be maintained, if possible, so that the infant may nurse at his mother's breast as soon as he is strong enough and mature enough. (For psychologic aspects of maternal nursing see p. 140.)

Human milk versus cow's milk feeding in relation to rickets in premature infants has been studied by Sydow (344) who found cow's milk superior to human milk in helping to prevent rickets in premature infants and in producing more nearly normal serum phosphorus and serum phosphatase levels even in infants who develop rickets. (See pp. 163, 327.)

Nutrition

Whether human milk or cow's milk is used, the amount as well as the kind of food that the premature infant can take is limited by the handicaps inherent in his prematurity, as is brought out by Levine and Gordon. "Because of weak sucking reflexes, easy fatigability, poor gag and cough reflexes, and the readiness with which respiratory embarrassment, abdominal distention, and diarrhea may be produced in premature infants, it is obviously better practice to feed the minimum amount of food and fluid which will result in satisfactory weight gains than the maximum amounts which the patients can tolerate (204)."

Feeding premature infants

Because of physiologic handicaps due to immaturity and rapid growth the premature infant (1) should be given food so constituted as to meet his peculiar needs; (2) should be given the minimum amount of food and fluid that will meet the caloric and water requirements and yet result in satisfactory weight gains; and (3) should be fed by one of several special methods, the selection being based on individual maturity and vigor.

MILK AND MILK MIXTURES

Table 47 shows milk mixtures designed to provide 120 to 132 calories per kg. that are suitable for feeding small premature infants—high in protein, low in fat, and high in calcium and phosphorus—and milks suitable for feeding larger premature infants. The composition of three standard mixtures and of human milk is given, as are the percentages of the total calories supplied by each of these components.

Changes in caloric value from 120 calories per kg. of body weight to lower caloric values for the smaller infants may be made by using appropriate amounts of the standard formula and adding water to bring the total fluid to 150 cc. per kg. For example:

To provide for a 2-kg. infant 90 calories per kg. from the standard half-skimmed milk and sugar mixture the calculation is as follows:

- 1. One cc. of the mixture will provide 0.9 calory per kg.
- 2. The amount of the formula required per kg. is obtained by dividing 90 (the calories required) by 0.9 (the caloric value of 1 cc.); the amount thus obtained is 100 cc. per kg.
- 3. Since the infant weighs 2 kg. he requires twice 100 cc., or 200 cc., of the milk mixture.
- 4. The total fluid requirement is 150 cc. per kg. Since the infant weighs 2 kg., the fluid requirement is twice 150 cc., or 300 cc.

The formula provides 200 cc. of fluid. Therefore 100 cc. of water must be added. If the infant cannot take the whole 300 cc. of fluid by mouth, all or part of the 100 cc. of added water may be given parenterally.

Gordon' (117) gives an illustration, shown in table 48, of the method of gradually increasing the food intake during the first week for a healthy infant weighing 1,500 gm. at birth and taking the powdered, half-skimmed milk mixture in which 20 percent of the calories are supplied by protein, 16 percent by fat, and 64 percent by carbohydrate. (See table 47.)

With regard to premature infants other than the 1,500-gm. healthy infant whose requirements are shown in table 48, Gordon (117)

Premature Infants

TABLE 47

Composition of milk mixtures for feeding premature infants designed to provide 120–130 calories per kg. of body weight (compiled in cooper-ation with Harry H. Gordon, M. D.)

		Protein		Fat		Carbohydrate		Calories	
Milk mixture 1 (per kg.)	Gm.	Percent of cal- ories	Gm.	Percent of cal- ories	Gm.	Percent of cal- ories	Total	Per cc.	
For smaller premature infants—less than 2,000 gm. (4 lb. 7 oz.): Half-skimmed milk, 180 cc., plus sugar, 15 gm. (approximately 10 percent added) Half-skimmed milk, powdered, 18 gm.,	5.3	16	2 .6	18	21.8	66	132	0.9	
total of 150 cc	6.0	20	2.2	16	19.4	64	121	.8	
gm. (4 lb. 7 oz5 lb. 8 oz.): Evaporated milk, 70 cc., plus sugar, 6 gm., plus water to make total of 150 cc Human milk, 180 cc	4.8 2.2	16 7	5.5 6.7	41 50	12. 9 12. 9	43 43	120 121	.8 .7	

¹ Acidification of milk with lactic acid is recommended for premature infants by some authorities. Theo-retically it would be indicated because of the tendency for these infants to have low gastric acidity. Prac-tically, lactic acid milk has the advantage of keeping for 24 hours without refrigeration.

comments:

"It is important that a schedule such as this be used only as a base from which one individualizes the feeding of each infant according to his ability to ingest and retain the amounts offered. For infants of less than 1,500 gm. it may be important to offer less than proportionately smaller amounts. For example, an infant of 1,200 gm. might be considered as entitled on a weight basis to 80 percent of the amounts Actually, he may tolerate only half of the amounts indicated. offered. Conversely, larger infants may be able to take more than proportionately greater amounts. In the case of very small infants, below 1,000 gm., it may be advisable to give nothing by mouth for the first 24, 48, or even 72 hours and to make up the fluid requirements of approximately 100 cc. per kg. per day wholly by the parenteral route.

. Ag e	5% glucose (cc. per feeding)	Water (cc. per feeding)	Feeding mixture (cc. per feeding)	Total fluid (cc. per kg. 24 hr.)	Total calories (per kg. 24 hr.)
0-12 hr 12-24 hr 24-36 hr 36-48 hr 36-48 hr 3, 4, 5 days. 6, 7 days. 8 days.	0 8 8 0 0 0	0 0 0 8 5 0	0 0 4 8 12-16 20-25 30	<pre> 1 20 1 20 75 105-135 135-160 160 </pre>	(1) 50-70 85-105 125

 TABLE 48 Initial feedings every 3 hours for infant of 1,500 gm. (Gordon)

¹ During the first 24 hr. no particular attention needs to be paid to the total fluid or the total caloric requirement.

Powers (277) has pointed out the advantages of comparing cow's milk mixtures on the practical basis of percentages of the calories supplied by the various ingredients, as is done in table 47. For premature infants he has used successfully for many years half-skimmed milk plus 10 percent sugar. The following table illustrates the method

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			Calories		
Constituents	Gm.	Calories per gm.	Number (col. 1 multiplied by col. 2)	Percent	
Total calories in 150 cc. of half-skimmed milk plus 15 gm. of sugar			131. 8	100	
Protein . Fat Carbohydrate in milk plus added carbohydrate	5.3 2.6 21.8	4 9 4	21. 2 23. 4 87. 2	16 18 66	

of computing percentages of calories derived from the various ingredients in the half-skimmed milk plus 10 percent sugar mixture:

In such half-skimmed cow's milk mixtures a very large proportion of the calories is furnished by carbohydrate, a form of energy readily utilized by the premature infant. The proportion of the calories supplied by protein is much larger and the proportion supplied by fat is much smaller in half-skimmed cow's milk than in an equal amount of human milk. Such mixtures therefore meet the peculiar need of small premature infants to derive their dietary calories preferentially from protein and carbohydrate because of their poor absorption of fat.

¹ Powers has added to his mixture of half-skimmed milk and 10 percent carbohydrate a sodium-citrate solution, water, vitamins of the B complex, and vitamin C. (Personal communication from G. F. Powers, M. D., Professor of Pediatrics, Yale University School of Medicine, New Haven, Conn., Nov. 7, 1946.) Darrow says that before the sodium citrate was added to the formula some of the younger premature infants had developed acidosis without abnormal stools. As ordinary milk mixtures contain more chloride than sodium he thinks the acidosis was "probably due to the inability of the kidneys to excrete as acid a urine as they will be able to later. The sodium citrate adds enough sodium to correct this defect. Actually I am not sure that it is important. We also added enough water to make renal function somewhat easier."

The amount of each component in 100 cc. of Powers' "sodium-citrate stock formula," which contains 78 calories [0.78 calory per cc.] is given by Darrow as follows:

Half-skimmed milk	83 cc.
Water	15 cc.
Sodium-citrate solution	2 cc.
Dextrimaltose	10.0 gm.
Thiamine	1.0 mg.
Riboflavin	2.5 mg.
Niacin	5.0 mg.
Ascorbic acid	25.0 mg.

The sodium citrate is a 6 percent solution; 20 cc. contains 12 meq. of sodium, or the equivalent of 1 gm. of sodium bicarbonate. (Personal communication from D. C. Darrow, M. D., Yale University School of Medicine, Dec. 12, 1946.)

Form of added carhohydrate

As is shown in table 46, human milk contains 7.50 percent carbohydrate and cow's milk, 4.75 percent; both are in the form of lactose. Carbohydrate may be added to milk mixtures in various forms such as lactose, cane or beet sugar, mixed sugars (dextrine and maltose), and corn sirup. There appear to be no definite advantages in the use of any one of these sugars in feeding premature infants. Granulated sugar and corn sirup are relatively cheap and readily available.

Following are the quantities of different kinds of sugar that weigh 30 gm. (approximately 1 oz.):

Cane or beet sugar	2	level tablespoonfuls
Milk sugar (lactose)	3	level tablespoonfuls
Dextrimaltose	4	level tablespoonfuls
Corn sirup	2	tablespoonfuls

Amounts of water and of milk

It is generally agreed that no fluids (neither water nor milk) should be given by mouth for at least 12 to 18 hours, and in some instances for 24 hours or longer after birth, since in this period the premature infant is likely to have respiratory difficulties, which may be increased by attempts at feeding. For smaller infants milk feedings should not be begun until 24 to 48 hours or even 72 hours after birth, the interval being longer for the less vigorous infant. For the smallest infants and for those who appear dehydrated it may be necessary to give fluid parenterally (subcutaneously or intravenously) in this early period. Usually it is safe to give larger and more vigorous premature infants fluid by mouth at the end of 12 hours.

After 12 to 24 hours small amounts of water may be given, followed about 12 hours later by initial milk feedings of 2 to 4 cc. for the smallest infants; 4 to 5 cc. for the larger and more vigorous infants: and 8 to 10 cc. for the largest and most vigorous infants. The amounts given at each feeding should be increased very gradually during the first weeks of life.

In calculating the amount of milk mixture to be given the total volume of fluid and the caloric value suitable to the age and vigor of the infant must be carefully considered. Toward the end of the first week the total amount of fluid required daily is 105 to 135 cc. per kg. As has been pointed out, the caloric requirements are of no concern in the first 2 or 3 days of life. The basic requirement of 50 calories per kg. may be met by the third to the fifth day, and the calories may then be gradually increased until the infant receives about 90 (80–105) calories per kg. at the end of the first week and 120 to 130 calories per kg. at the end of 10 days or 2 weeks. The daily milk mixture requirement is about one-fifth to one-seventh of the body weight. If the milk feedings do not provide the total fluid required, additional water must be given by mouth or parenterally.

Intervals of feeding

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

The very small, feeble infant who must be fed by gavage may be fed less often and given somewhat larger amounts than the infant fed by medicine dropper. The same rules should be observed, however, in regard to total amount of daily feedings and caloric requirements.

It should be emphasized that, in the first days of life particularly, there is great variation in the needs and the tolerance of premature

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infants. The physician will best be able to decide, on the basis of his clinical experience, what each infant needs after due consideration of birth weight, degree of maturity, and general condition.

Methods of administration of feedings

Premature infants may be fed by gavage, medicine dropper, or nursing bottle, depending on their vigor. The nurse's record of an infant's feeding behavior may indicate that a change from one method to another is desirable. (For medical and nursing records see appendix 5, p. 376.) Whatever method is used the infant's head and shoulders should be raised while the feeding is being given.

For the smallest infants who are unable to suck or have feeble sucking and swallowing reflexes tube feedings (gavage by catheter) are necessary and in some clinics are always given to infants of less than a certain birth weight. It should be pointed out that gavage is by no means a simple method of feeding and must be done by a skilled individual. (For technique of gavage feeding see appendix 6, p. 386.) If it is not properly done it may cause trauma of the upper gastrointestinal tract, or milk may be regurgitated and enter the respiratory tract. On the other hand, when properly done it is often a life-saving measure. An infant weighing at birth 662 gm. (1 lb. 7 oz.) is reported by Levine and Gordon (204, pp. 299, 302) to have been fed entirely by gavage for the first 61 days of life with no untoward effects.

For infants in the intermediate group $(2\frac{1}{2}$ to $4\frac{1}{2}$ lb.) feedings may usually be given by medicine dropper with rubber tip until the infant sucks vigorously on the rubber tip, after which a bottle with a small nipple may be used. The Breck feeder should never be used since forcing milk into the infant's mouth before he is able to suck is extremely dangerous.

The largest and most vigorous infants, after initial trial with medicine-dropper feeding, may be found to suck well and may be fed by bottle.

Nursing at the breast should not be attempted until the infant is sufficiently vigorous to be treated as a full-term infant. Efforts to maintain the mother's milk supply should be made, however, especially for infants born near term.

The milk mixtures for the premature infant, as for any infant, should be prepared under the most favorable conditions to assure sterility of the mixture, the bottles, and the nipples. (See **360**.)

ADMINISTRATION OF MINERALS

The healthy premature infant whose feeding is modified cow's milk needs no supplementary minerals in the early weeks of life. There is some evidence, however (see p. 151), that premature infants whose diet is based on human milk need supplementary calcium and phosphorus. Calcium caseinate (a dried-curd preparation) will supply both these minerals and will also increase the amount of protein an advantage for the premature infant. The addition of calcium caseinate is especially indicated if the infant has a tendency to diarrhea. Skimmed lactic-acid milk is also used to add calcium, phosphorus, and protein to breast milk. Hess and Lundeen (148, p. 105) suggest the use of calcium caseinate in the proportion of 2 percent of the human-milk feeding or one part of skimmed lactic-acid milk to three parts of human milk.

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It is not necessary to supplement the premature infant's diet with iron during the neonatal period. (For prevention of anemia in premature infants see pp. 152, 301.)

ADMINISTRATION OF VITAMINS

The premature infant does not get enough of any vitamin in his feeding of either human milk or cow's milk to meet his special requirements. For this reason his total vitamin needs must be met by supplements to his diet.

Vitamin A

For infants 6 to 8 months of age the amount of vitamin A recommended by the National Research Council is 1,500 international units daily (242). Though the requirement for the premature infant has not been definitely established, his diet needs ample supplementation with vitamin A beginning in the first week of life. Milk contains vitamin A, but this source is not adequate to meet the premature infant's requirement because of the small amount taken, and the infant's poor absorption of fat or the low-fat milk mixture that he is given.

Vitamin A is usually given in combination with vitamin D, and the amount that will provide sufficient vitamin D for premature infants will also fill the requirement for vitamin A. The amount of percomorph oil or its equivalent (20 drops, to be increased to 30 drops after 5 days if tolerated) recommended for premature infants by Davison (78, sec. 242), for example, would provide at first approximately 25,000 or more international units of vitamin A and 3,600 units or more of vitamin D, and later, 37,500 units of vitamin A and 5,400 units of vitamin D. Warkany (377) gives 20,000 to 50,000 international units as the amount of vitamin A that may be required in disorders involving disturbed fat absorption. He does not mention premature infants in this connection, but the defective fat absorption of many premature infants, particularly small ones, suggests the applicability of these amounts to their prophylactic need.

Clifford (66) has shown that the absorption of vitamin A by premature infants is greatly increased when it is given in a nonoil menstruum miscible in water or milk. If vitamin D is given parenterally or in massive doses a separate preparation of vitamin A will of course be necessary. (See vitamin D, p. 178.)

Vitamin-B complex

The daily prophylactic requirement of the vitamin-B complex has not been established, and the daily requirement of its best-known components—thiamine, riboflavin, and niacin—has been established only for full-term infants and not for premature infants. For infants 6 to 8 months of age the National Research Council recommends daily allowances of 0.4 mg. of thiamine, 0.6 mg. of riboflavin, and 4.0 mg. of niacin (242).

The needs of premature infants are probably greater than those of full-term infants. These components are not stored to any extent in the body, the small amount of milk taken probably does not contain them in protective amounts, and deficiencies may develop rapidly in the premature infant. Moreover, a diet high in carbohydrate, like

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that of the premature infant, may increase the need for thiamine. Administration of the vitamin-B complex is probably indicated for these reasons and for the further reason that its other components, about which less is known, may have important functions in nutrition, especially in relation to the utilization of amino-acids. (See p. 156.)

The vitamin-B complex is especially needed if the infant is suffering from diarrhea. Litchfield and associates (211) consider it possible that the injection of large amounts of water in the presence of dehydration "may be really harmful unless the vitamin-B complex is given at the same time."

The vitamin-B complex may be given in the form of yeast tablets or yeast powder, which are miscible in water or milk, or yeast extract. It may also be given combined with other vitamins.

Ascorhic acid (vitamin C)

The daily requirement of ascorbic acid (vitamin C) for infants of 6 to 8 months is 30 mg., according to the National Research Council (242). Both human milk and cow's milk contain variable amounts of vitamin C; but since for feeding premature infants both are boiled, a process that destroys a large part of the vitamin C, the premature infant's diet, whether human milk or cow's milk, should always be supplemented. It should be noted also that according to Levine and Gordon (204, p. 308) "an increased daily supply of the vitamin is necessary when premature infants are fed cow's milk mixtures of high protein content."

Gordon (116) says: "Because premature infants are born with low stores of vitamin C and because they frequently have spontaneous hemorrhages it is probably advisable to give ascorbic acid, particularly to small infants, during the first days of life. No information is available as to the proper dose, but 100 mg. daily for the first 2 or 3 days seems a reasonable guess." After this the dose should be reduced to 50 mg. and continued at this level until the infant reaches a weight at which prematurity is no longer a problem.

Levine has established for the New York Hospital clinic a routine prophylactic dose of ascorbic acid for premature infants as follows: 25 mg. begun at the end of the first week, increased gradually to 50 mg. and maintained at this level throughout the infants' stay at the hospital. (Personal communication from S. Z. Levine, M. D., New York Hospital, New York, Dec. 27, 1946.)

Vitamin C should be given to premature infants in concentrated form, ascorbic (cevitamic) acid in a small amount of water or milk, since they cannot take sufficient amounts of orange juice to meet their requirements. To obtain 50 mg. of vitamin C from orange juice 100 cc. $(3\frac{1}{3}$ oz.) is required. In the form of ascorbic-acid tablets 50 mg. can be given dissolved in 10 cc. of water. Giving it with or just after feedings is said to make for better absorption. "It may be administered parenterally in concentrated form as sodium ascorbate when persistent vomiting, diarrhea, or other conditions prevent the utilization of proper amounts taken orally (18, p. 495)."

There is probably some advantage in gradually shifting from synthetic ascorbic acid to orange juice as soon as the infant is able to take enough for his needs, because orange juice contains vitamin P as well as vitamin C. (See p. 167.)

Vitamin D

The daily allowance of vitamin D recommended by the National Research Council for infants 6 to 8 months of age is 400 to 800 international units (242). The amount recommended for premature infants varies from the 800 international units recommended by Jeans and Marriott to the 1,000 to 10,000 units or more recommended by Park and others (see p. 162.) At the New York Hospital unit for premature infants the routine daily prophylactic dose is 2,000 international units. In view of the special susceptibility of premature infants to rickets (see p. 323) and the finding of toxic effects only after administration of enormous doses of vitamin D (see p. 164), the larger prophylactic doses seem to be indicated, beginning in the first week and continuing during the early period of most rapid growth.

Cod-liver oil and other fish-liver oils, which are commonly given to full-term infants for their vitamin-D and vitamin-A content, should not be given to small or weak premature infants because of the danger of aspiration and resultant lipoid pneumonia. They are particularly dangerous for the smallest and weakest infants. The concentrate of vitamins D and A that is used for premature infants should be one that is miscible in water or milk. For very small infants or for infants suffering from diarrhea it may be advisable to give vitamin D_2 or D_3 parenterally.

The use of massive prophylactic doses of concentrated vitamin D has been reported to be effective against the development of severe rickets and in most cases against slight rickets, without resulting toxicity. The single doses varied from 200,000 to 600,000 international units (usually 500,000-600,000 units). Massive-dose prophylaxis for premature infants is being used in a clinic in Stockholm as a routine measure. (See p. 165.)

Vitamin K

Vitamin K (2 methyl-1, 4-naphthoquinone) is a fat-soluble vitamin commonly known as menadione. It may be given orally. In water-soluble form it is also available for parenteral use and in special ointment for use as an inunction.

If possible, the mother should receive vitamin K during pregnancy or labor. The consensus of opinion is that the premature infant should receive vitamin K immediately after birth, whether the mother has or has not received the vitamin.

Hellman recommends for the mother a 1-mg. tablet of synthetic vitamin K daily during the last 2 weeks of pregnancy. On admission to the hospital in labor or shortly before labor, if the mother has not previously had vitamin K, she is given 4.8 mg. intramuscularly, and this dose is repeated daily until delivery. All premature infants are given 2.4 mg. intramuscularly at birth. (Personal communications from L. M. Hellman, M. D., Department of Obstetrics, Johns Hopkins Hospital, Baltimore, Oct. 8 and Nov. 10, 1947.) Poncher (266) suggests a dose of 5 mg. for the premature infant, repeated if there is clinical evidence of hemorrhage, no matter how slight. (See Hemorrhagic Disease, p. 292.)

Vitamin P

No published reports on prophylactic administration of vitamin P have been found. Rutin is now being administered to premature

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infants at Johns Hopkins Hospital on an experimental basis. (Personal communication from Janet Hardy, M. D., Department of Pediatrics, Johns Hopkins Hospital, Baltimore.) (See p. 167.)

Summary

Infants born prematurely have certain nutritional handicaps because the various mechanisms for ingestion and digestion of food are not fully developed. In addition, the demand for certain elements is increased because of these infants' rapid growth and inadequate antenatal storage.

Information in regard to all the nutritional needs of premature infants is not available, but certain needs have been determined on the basis of balance studies and others by clinical trial.

The protein requirement of the premature infant is greater than that of the full-term infant. The daily allowance recommended for premature infants weighing less than 2,000 gm. (4 lb. 7 oz.) is 6.0– 4.4 gm. per kg. (2.7–2.0 gm. per lb.); for those weighing 2,000 gm. or more, 5.0–4.4 gm. per kg. (2.3–2.0 gm. per lb.).

Many premature infants, especially those who are smaller and more immature, have difficulty in absorbing fat. Fat absorption has been found to be more nearly complete when half-skimmed milk (about 2percent fat) is used.

The premature infant tolerates carbohydrate well. When the fat content of the feeding mixture is low, carbohydrate may be added to provide the necessary calories.

The daily caloric requirements of premature infants are relatively low—the maximum from approximately 2 weeks of age being 120 to 132 calories per kg. (55–60 per lb.) of body weight.

The daily fluid requirement has been found to be about 150 cc. per kg. (70 cc. per lb.), rarely exceeding 160 cc. If the premature infant cannot take enough fluid by mouth to meet the calculated requirement, parenteral administration of fluid is indicated to prevent or combat dehydration and to maintain the electrolyte balance.

The premature infant's need for calcium and phosphorus is greater than that of the full-term infant. Cow's milk, which contains 0.122 percent of calcium and 0.090 percent of phosphorus, has been found to meet the requirements of premature infants.

Iron given in the neonatal period has not been found effective in preventing early anemia. In the second or third month after birth supplements of iron are usually needed as prophylaxis against an irondeficiency anemia.

The premature infant's diet in the neonatal period consists of milk. Cow's milk has been found to meet the peculiar requirements of these infants because it has a higher content than human milk of protein and of calcium, phosphorus, and other minerals and because the fat can be readily skimmed. Human milk also can be modified to meet the requirements.

The daily rate of gain in weight of premature infants fed on halfskimmed cow's milk in the neonatal period has been found to be greater than the gain on unmodified human milk or on evaporated whole milk. The difference in the gain on the different feedings was especially striking among the smaller infants. Among the larger infants it was insignificant, so that for psychological reasons the authors suggested the use for larger premature infants of their own mothers' milk followed by breast feeding when they were able to suck.

As the premature infant approaches maturity the feeding requirements approach those of full-term infants. Nursing at the breast should then be encouraged, or whole cow's milk mixtures may be used.

The formula should be prescribed to meet the known protein, carbohydrate, and fat requirements as well as the caloric and fluid requirements. For example, a standard mixture of 150 cc. of halfskimmed milk with 10 percent of added carbohydrate (15 gm., or $\frac{1}{2}$ oz.) will provide 5.3 gm. of protein, 2.6 gm. of fat, and 21.8 gm. of carbohydrate. The caloric content will be 132 calories of which protein will provide 16 percent; fat, 18 percent; and carbohydrate, 66 percent. The mixture will provide 0.9 calory per cc., or 27 calories per oz.

The age at which water and milk may be given and the amount per feeding that can be taken are related to the size and vigor of the infants. It is generally agreed that no water or milk should be given for 12 to 18 hours after birth and in some cases for 24 hours or even longer. Initial feedings of either milk or water should be very small, 2 to 4 cc., and the amount should be increased gradually until, when the infant is 10 days to 2 weeks old, it has reached the fluid and caloric content of the standard mixture described, which is then maintained.

It may be necessary in the early neonatal period to feed small premature infants every 2 hours. Larger or more vigorous infants may be fed every 3 or every 4 hours.

The method of administering the milk mixture depends on the vigor of the infant and his ability to suck. If the sucking and swallowing reflexes are absent or weak, feedings should be given by gavage until the infant sucks vigorously on the catheter. A medicine dropper with rubber tip can then be used. Bottle feedings may be given when the infant becomes more vigorous. A premature infant should not be put to the breast until he has attained the vigor of a full-term infant.

Milk mixtures should be so prepared as to assure the sterility of the mixture, the bottles, and the nipples.

The premature infant's prophylactic and therapeutic requirements of vitamins are greater than those of the full-term infant, but the amounts required for prevention and for treatment of deficiencies have been established only in part, the knowledge of treatment being especially incomplete. This incompleteness as to treatment places all the more emphasis on the need to apply in the care of the premature infant, the knowledge that is available as to the always important preventive aspect.

The premature infant cannot get sufficient vitamins from the small amount of milk that he is able to take in the neonatal period, and he should have his entire daily vitamin requirements in the form of supplements to the milk feeding. Vitamins A, C, and D, and probably the vitamin-B complex should be given early, in adequate amounts, and in concentrated form. The recommended allowance of vitamin C (ascorbic acid) is 50 mg. daily; of vitamin D, 800 to 10,000 international units daily, or massive doses at monthly or longer intervals. The daily requirements of vitamin A and of the B complex and its components have not been determined. It is now recommended that vitamin K should be given to pregnant women before or during labor

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and to the premature infant whether the mother has received it or not. The suggested dose for the mother is 1 mg. daily by mouth for the last 2 weeks of pregnancy or 4.8 mg. intramuscularly on admission to the hospital, repeated if the interval before delivery is more than 24 hours. For the premature infant the dose suggested by different authorities is 2.4 mg. or 5 mg. intramuscularly immediately after birth.

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CONGENITAL MALFORMATIONS

Premature infants may be born with any type of malformation, and congenital malformations rank relatively high among the causes of death of these infants. No information has been found as to the incidence of various types of malformation among premature infants nor on their rate of survival.

Many premature infants die of defects that are amenable to surgical treatment if promptly diagnosed. For this reason major defects that are thus amenable to correction will be discussed in some detail.

Diagnosis, except for obvious gross defects, is usually difficult, especially if the infant is small and feeble. Complete physical examinations and laboratory procedures are often in themselves hazardous to the infant. They must be made, however, if the infant's life is to be saved, and they must be made with a minimum of trauma and without exposure of the infant to unfavorable environmental conditions.

In addition to early diagnosis, premature infants with serious congenital defects must have skilled surgical treatment, skilled pediatric supervision, and skilled nursing care. To operate on a premature infant obviously requires more skill than to operate on a mature infant. Special skill on the part of the pediatrician is needed, too, not only in diagnosis but in the joint decision with the surgeon on the most favorable time to operate and in the supportive treatment to maintain body temperature and nutrition and to meet fluid requirements that is as much a part of the program to save the infant's life as is the operation.

A congenital malformation may occur in any organ er part of the body as the result of fetal maldevelopment. The malformation may be (1) minor, i. e., of such a nature that it impairs function only slightly or not at all or (2) major, i. e., incompatible with life or requiring repair by major operative procedure. The term "monster" is sometimes applied to a fetus or infant (124) who, "through congenital faulty development, is incapable of properly performing the vital functions, or who, owing to an excess or deficiency of parts, differs markedly from the normal type of the species." The use of the term, however, seems undesirable because it furnishes no information as to the type or extent of the defects.

Causes

Recurrence of various congenital defects in different generations of the same families has been reported for many years, as has the occurrence of a congenital defect in only one member of a family previously normal. It is generally agreed that many defects are due to heredity, but some investigators record the influence of environmental factors, especially in experiments with animals. Warkany (376) states: "... the repeated occurrence of a defect ... does not prove that it is genetically determined, since several members of a sibship may be exposed to the same pathogenic environmental factors." On the other hand, a defect may be "genetically determined," even though it occurs in only one member of a family. As early as 1908 Mall (218) said: ". . . we must divide monsters into two groups, those in which the proper conditions to produce them are already in the germ (are therefore inherited) and those due to certain external influences which act upon the egg after it is fertilized." In reaching this conclusion Mall recognized the importance of animal experimentation, by means of which extensive and important research on this subject has continued to be done in recent years. Environmental factors that have been shown to have an influence on congenital malformations in human beings are maternal pelvic irradiation, certain maternal diseases, and perhaps maternal diet.

Murphy (241, p. 113) reaches the following general conclusions from his study of congenital malformations:

"Until further evidence is forthcoming, the observations assembled in the present volume make the two following statements seem justified:

"(a) When a congenital malformation has a genetic basis, there is a greatly increased chance that subsequent brothers or sisters also will be malformed.

"(b) When a congenital defect is due to factors that are not genetic in origin, offspring conceived subsequently should be congenitally malformed only with the same frequency as is commonly observed in the population at large."

INHERITED TENDENCIES

Murphy: (241) believes that genetic factors were the most likely cause of all the congenital malformations studied in his series, though he comments on the difficulty of making a complete separation of the environmental from the hereditary factors. He says (p. 78) that "both maternal irradiation and maternal rubella can play a very definite role in influencing fetal development"; but he found no evidence that any of the mothers of malformed children in his series had had either irradiation therapy or rubella. He concludes (p. 79)that "congenital malformations, as they appear in a random sample of the population, arise from factors inherent in the germ cells prior to fertilization."

Murphy based his conclusions (p. 8) on study of 890 live-born and stillborn infants for whom death certificates were issued in Philadelphia during the 5 years 1929–33 and for whom the diagnosis of congenital malformation was confirmed, and of 45 other infants having congenital malformations discovered through home visits. Siblings, age of mother, order of birth, and other characteristics in varying numbers of the families of these 935 infants were studied in relation to congenital malformations. Some of the conclusions follow (pp. 81, 82).

^aIn families already possessing a malformed child the birth of a subsequent malformed offspring takes place with a frequency which is in the neighborhood of 25 times greater than that of the general population.

"In families possessing two or more malformed siblings the defect in the subsequent offspring was identical with that in the previous defective sibling in approximately 50 percent of instances.

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"The older the mother the more likely she is to give birth to a congenitally malformed child.

"The child born later in a family is more likely to be congenitally malformed than is an older brother or sister."

ENVIRONMENTAL FACTORS

Influence of radium and roentgen therapy

Murphy (240) pointed out that human growth is arrested through exposure of the pregnant woman to therapeutic radium or roentgen irradiation. He found that among the children of 402 women given preconceptional pelvic irradiation 7 had gross deformities, and among the children of 74 women given postconceptional irradiation, 25 were deformed. These figures are included in a study of 625 pregnancies of women subjected to pelvic radium therapy or roentgen irradiation, which was based on published reports and on returns from a questionnaire sent to more than 1,700 leading gynecologists and radiologists.

Influence of maternal disease

Attention was first drawn to the association between *rubella* in the mother during pregnancy and fetal congenital malformations by the report of Gregg (127) in 1941. Of 78 infants with congenital cataract, 68 were born to mothers who had had rubella (German measles) in the early months of pregnancy. In 44 of these infants a congenital heart lesion was also present. Swan and his coworkers (339, 340) made two studies on this subject in South Australia together covering the years 1939 through 1943. According to combined figures from the two reports, 61 mothers had had rubella at some time during their pregnancy, 41 of whom gave birth to congenitally defective infants. All 30 mothers who had rubella in the first 2 months of their pregnancy gave birth to defective infants, compared with 6 of the 10 who contracted the disease in the third month and 4 of the 18 who contracted the disease after the third month. Sixteen of the 41 defective infants had eye defects, of which 15 were cataracts. Ten of the 16 infants with eye defects also had congenital heart lesions, as did 11 other infants. Twelve infants suffered from deaf-mutism.

Conte, McCammon, and Christie (67) summarized as follows the results of studies (127, 339, 340, 288, 98, 257) on maternal rubella and its association with congenital anomalies in the infant:

"One hundred and thirty-four cases have been reported in the literature in which maternal rubella in pregnancy was followed by congenital abnormalities. In all but 3 of these cases the rubella occurred in the first trimester of pregnancy." The defects most frequently reported were cataracts and heart anomalies. Mental retardation or defect is mentioned as common, but there is no record of any testing techniques by which this was determined. Other anomalies found in these published reports were deaf-mutism, microphthalmos, and microcephaly, and 1 case each of hypospadias and obliteration of bile ducts.

Twenty cases of maternal rubella that were not associated with congenital malformations were included in the combined series cited by Conte and associates (67). None of these occurred in the first 2 months of pregnancy; 4 occurred in the third month.

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Among the investigators cited by Conte and associates, Swan was the only one to report the occurrence of deaf-mutism in association with maternal rubella; but as more older children have been examined this defect has been reported to be of very frequent occurrence. Carruthers (61) stated that of 102 congenitally defective children born of mothers who had had rubella 74 were deaf, and he gives a detailed report on 18 such children, who suffered severe but not always complete deafness with associated muteness.

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Gregg (chairman) and his coworkers (126) on a committee appointed by the Governor General of Public Health of New South Wales in 1944 to study this subject collected the histories of the mothers of 148 congenitally defective children and found that in 130 cases there was a history of a maternal exanthem during pregnancy. In these 130 children the outstanding defects, occurring alone or in combination, were deaf-mutism (111 cases), heart disease (38 cases), and eye defects (23 cases). The committee also examined 53 children ranging in age from 1 year 7 months to 6 years 9 months, of whom 43 were "deaf with secondary muteness," 19 had congenital cardiac lesions, and 12 had eye defects.

Most of the examinations were made after the children had reached their fourth year and included tests by persons specially qualified to test blind and deaf children. The committee concluded that all but 4 of these children were educable and had good prospects of being able to earn their living. The committee report commented: "Before these children reached their third birthday it was the opinion of many medical practitioners that a large number were mentally defective, but apparently thought had not been given to the tremendous retardation which must occur in a young child when there is loss of sight or hearing."

Reports have appeared in the United States medical literature confirming the Australian findings. Not all studies, however, show association of maternal rubella with congenital defects in the offspring.

Conte and associates (67) comment, after reviewing some of the studies: "It is difficult to evaluate the significance of these reported cases because it is not known how often virus infections occur without congenital malformations or how often malformations occur without virus infections. In other words, there are no controls for the reported cases." In an effort to remedy this statistical defect the most recent reports attempt to study the condition epidemiologically. Conte and associates followed a series of 120 infants with various types of congenital defects and found only 5 in which there was a history of maternal rubella during pregnancy, all but 1 of these in the first trimester. The 5 infants had congenital defects, diagnosed as follows: 3-congenital cataracts, congenital heart disease, and cerebral aplasia: 1-congenital heart disease and mongolism; and 1-congenital cataracts and cerebral aplasia. As evidence that maternal rubella in the early months of pregnancy "is a predisposing cause of congenital malformation" the authors figured that the rubella case rate among their 120 cases of congenital abnormalities (4.2 percent) was "at least 10 times the actual case rate of maternal rubella for the child-bearing age-group in the population at large."

Results of investigation by Fox and Bortin (105) do not tally with those of previous studies. They investigated Milwaukee healthdepartment records of 22,226 cases of rubella reported in epidemics

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that occurred in the city during the 3 years 1942–44. Of 152 married women investigated 11 were pregnant at the time they had rubella. Of these 11 women 5 had the disease in the first 2 months, 4 during the second to the fourth month, 1 in the seventh month, and 1 in the ninth month. These was one stillbirth. None of the live-born infants were congenitally malformed.

Rones (294), after supplementing the records of Reese (288) and Swan with 4 cases from his own experience, observes: "It is not to be understood that all cases of congenital ocular abnormalities are due to an exanthematous disease in the mother during pregnancy. Undoubtedly many other factors can operate to produce such disturbances. . . . Rubella has been regarded as one of the most innocuous of the exanthematous diseases. We are now faced with the fact that the virus attacking a pregnant woman before the placental barrier has been developed can cause a disturbance to the developing fetus, and particularly to the optic buds."

The particular interest of these studies in relation to prematurity as determined on the basis of weight and the need for special care lies in the fact that many of the infants were reported to be small, even when born at or near term. In Gregg's first study (127) the average birth weight of all the infants whose birth weight was known was 5 lb. (2,268 gm.). For the 29 infants with congenital defects in the first series of Swan and his associates (340) for whom birth weight was reported the average was 5 lb. 7 oz. (2,466 gm.). Only 7 were reported by the authors to be premature, but 17 weighed 5 lb. 8 oz. (2,500 gm.) Nine of the 18 deaf mutes reported on by Carruthers (61) or less. weighed 2,500 gm. or less at birth. The New South Wales committee (126) noted in the series of 130 congenitally malformed infants born of mothers who had had rubella 14 premature deliveries and 105 deliveries at term, there being no information on this point in the other The average birth weight of the 130 infants was 5 lb. 15 oz. 11 cases. The birth weight of the infants born at term ranged (2,693 gm.). from 3 lb. 8 oz. (1,588 gm.) to 9 lb. 5 oz. (4,224 gm.), and only 27 infants weighed more than 7 lb. (3,175 gm.).

Toxoplasmosis is another, relatively rare, maternal infection that may cause congenital defects of the nervous system as well as other defects in the offspring. This disease, caused by protozoa of the genus toxoplasma, may be transmitted to the fetus in utero. Symptoms, predominantly of nervous system involvement, may be present at birth or appear a few days or weeks after birth. The symptoms are those of hydrocephalus or microcephalus, convulsions, muscular twitchings, spasticity, ocular palsies, and chorioretinitis. Roentgenograms show evidences of calcification and extensive destruction of brain substance. In addition there may be widespread visceral involvement shown by jaundice, splenic enlargement, and respiratory disturbances. That the condition is congenital may be confirmed by finding toxoplasmic antibodies in the maternal blood sera.

A higher than average incidence of congenital malformations has been found among infants of mothers with *diabetes mellitus*. Joslin (176) found congenital malformations in 17 percent of 125 such infants. Miller (233) reports 6 infants with one or more congenital malformations in 19 consecutive autopsies on infants born to diabetic mothers. White (396) comments on the high incidence of congenital malformations, "usually involving tissue which is mesenchymatous in

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origin," among such infants. She considered imbalance of the sex hormones to be the factor mainly responsible for the abnormal fetus, as well as for other conditions affecting survival and morbidity among these infants, and reported favorable results from diethylstilbestrol the progesterone therapy of the mothers. (See p. 24.)

Influence of maternal diet

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Murphy (241, p. 50) found a high incidence of dietary deficiencies during pregnancy among the 545 women who reported on their food habits, but he concluded that "it was not possible to correlate deficiencies in diet with the occurrence of malformed children." He did not study a control group.

Warkany and his coworkers have been able to produce in rats congenital skeletal abnormalities (380, 381, 382, 383, 384, 385, 374) as well as cleft palate (386) and deformed eyes (388 and 387) by administering deficient diets (rachitogenic Steenbock and Black diet supplemented with vitamin D to prevent rickets) to the females during pregnancy. In control groups on adequate diets no such malformations were found. It was found later that a supplement of 2 percent of dried liver in the maternal diet prevented these abnormalities, and the preventive substance was identified as riboflavin (375).

Warkany and Schraffenberger (387) experimented with female rats raised on a diet of a known small carotene content, bred on a highly purified diet free of carotene and vitamin A, and mated to normal males. The young of those who were able to produce living offspring were born blind and had deformed eyes. The young of the control group, who received the same diet supplemented with vitamin A, did not have these deformities. In a later report (388, p. 168) these authors observed that the newborn rats "had various defects of the skeleton and some of the soft tissues," as well as eye defects. "Histologic sections of the eyes were studied, and a fibrous retrolenticular membrane was found in place of the vitreous in every specimen." (See p. 336). Other eye defects noted (p. 169) were "colobomas, eversion and abnormal structure of the retina, rudimentary development of the iris and of the ocular chambers, defects of the cornea and of the conjunctival sac, and lack of fusion of the lids." With regard to coloboma the authors comment (p. 168) : "The fact that a malformation such as coloboma, which has been observed as a hereditary defect, can also be induced by maternal dietary deficiency is in agreement with the conception that a specific malformation can be the result of a genic mutation in one case and of an environmental modification in another." As in the previous experiment, the eyes of the young were normal when the maternal diet was supplemented with vitamin A during pregnancy.

These experiments show that congenital malformations in rats may be caused by defective maternal nutrition. According to Warkany (374), "it remains to be seen, however, whether similar maternal nutritional disturbances lead to congenital defects in man." In rats cleft palate has been due in some cases to genic influences, but it has also been brought about in experiments of Warkany and his associates (386, p. 884) by defective maternal diet. Though further study is needed, they regard it as probable, especially from studies that have been made of identical human twins, that "in human beings also, cleft palate can be due to modification as well as to mutation." They comment (**p. 894**):"... a high familial incidence of deformities does not necessarily indicate that they are genetically determined ... unfavorable environmental conditions can affect whole families, and thus their effects will imitate those of hereditary transmission ..."

Jackson and Kinsey (168), noting that in the studies of Warkany and Schraffenberger there was considerable variation in the degree of abnormality of the eyes in different litters of rats, used the techniques of these investigators in an attempt to determine what degree of deficiency of vitamin A would produce the malformations. Of female rats "grown to maturity without the accumulation of hepatic stores of vitamin A," and then bred and given only minimal amounts of the vitamin during pregnancy, those that "carried their fetuses to advanced stages of development" produced litters with the eye abnor-malities described by Warkany and Schraffenberger. Of other groups given 2, 3, 5, or 10 international units of vitamin A daily before breeding and during pregnancy, those receiving less than 3 to 5 international units daily had young with eye defects, whereas those receiving more than this amount all had young with normal eyes, even though the vitamin-A dosage was insufficient to permit normal delivery at term. The authors concluded that "ocular defects occur in the young rat only when the maternal vitamin-A deficiency is extremely severe. . . To the extent that the physiologic processes associated with reproduction in human beings parallel those in the rat it may be inferred that vitamin-A deficiency in the mother is not a probable cause of retrolental fibroplasia."

Burke and her associates (55, p. 580) found a significant relationship between prenatal diet and the condition of the infant at birth and in the first 2 weeks of life. Of the 33 infants in their series who were in the "poorest" physical condition, including those with marked congenital defects, 26 were born to mothers whose prenatal diet was "poor to very poor." Of the 12 infants with congenital defects (including 1 stillbirth and 4 premature infants) 7 (3 premature) were born to mothers whose prenatal diet was poor to very poor; 4 (1 premature), to mothers whose prenatal diet was fair or fair to poor; and 1 (a full-term infant with congenital heart disease), to a mother whose diet was excellent.

Incidence

Congenital malformations are believed to occur more frequently among premature than among full-term infants, though Potter and Adair (273, p. 16) did not find this to be true in a series of 526 fetuses and infants studied postmortem. In this series 26.8 percent of the 231 full-term infants (live-born and stillborn) were defective compared with 11.2 percent of the premature and "previable" infants (live-born and stillborn). (For the authors' definition of "previable" see p. 5.) On the other hand, Murphy (241, pp. 26, 27), after analyzing the information obtained from death certificates, hospital records, and home visits with regard to a group of 931 malformed infants (live-born and stillborn; miscarriages excluded), reported that 18.4 percent were premature, though only 4.5 percent of their 1,738 normal siblings were premature. He comments: "The significant finding with regard to the duration of pregnancy is the fact that the malformed offspring

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were born prematurely more than four times as often as were their normally developed siblings. . . ."

In a Children's Bureau study of 999 consecutive births, 938 births were those of live-born and 61, of stillborn infants. Among the 938 live-born infants major defects (defects severe enough to endanger the infant's life or severely handicap him) were found in 4.6 percent (3) of the 65 premature infants, compared with 2.4 percent (21) of the mature infants. Of the stillborn infants 34 were mature and 27 premature. Among the live-born and stillborn infants considered together major defects were found in 9.8 percent (9) of the 92 premature infants, compared with 2.4 percent (22) of the 907 mature infants. (Unpublished data collected in New Haven, Conn., 1928-30.)

In regard to the incidence of the various types of minor and major malformations in live-born premature infants no data appear to be available. DePorte and Parkhurst (81), however, have reported the information for a large series of infants (maturity not specified) born in New York State, exclusive of New York City, in 1940–42. According to their figures (which follow), based on birth certificates, defects of the central nervous system comprised the largest group of defects— 22.4 percent.

Congenital malformations, total	1 3, 635
Spine hidde	480
Spilla Dillua	159
Noningsoole and encompalaçale	102
A noncorbalua	00
Anencephatus	66 90
Welfermetions of the beest	
Mailormations of the near the second second second	142
Other manormations of the cardiovascular system	4
Mailormations of the digestive system	120
Mairormations of the genitourinary system	52
Monstrosity	11
	D4
Abdominal evisceration	40
Malformations of the head	6
Mailformations of the eye	25
Malformations of the ear	23
Malformations of the nose	7
Malformations of the jaw	4
Achondroplastic dwarf	12
Osteogenesis imperfecta	5
Scoliosis and other spinal deformities	5
Torticollis	9
Congenital dislocation of the hip	4
Clubfoot	584
Other foot deformities	109
Deformed leg or knee	34
Deformed or underdeveloped hand or arm	82
Hand, foot, arm, or leg missing	29
Adactylism, polydactylism, syndactylism	278
Harelip, cleft palate	336
Congenital tumors	77
Hemangioma and nevi	79
Developmental defects of the external genitalia	264
Defects of the superficial tissues	130
Tonguetie	9 9
Cyanosis, cause unknown	39
Others and unspecified	155

¹These malformations were found by DePorte and Parkhurst in 3,180 children, of whom 41 also had a birth injury; figures based on birth certificates.

Premature Infants

On the basis of information from death certificates, DePorte and Parkhurst (81) found an even greater incidence of defects of the nervous system (37.5 percent); and in the study by Murphy (241, p. 63) of 935 malformed infants, for 890 of whom the information was obtained from death certificates and confirmed from other sources, the nervous system was found to be involved in 566 (60.5 percent). (Murphy's study included 760 full-term and 171 premature infants, liveborn and stillborn, 3 miscarriages, and 1 infant for whom information as to maturity is not given.) The relative frequency of the various types of defects of the nervous system reported by Murphy is shown in table 49.

TABLE 49	Frequency of various infants (Murphy)	defects of	the nervous	system	among	malformed

Defect of nervous system	Number	Percent
Total reported	566	100.0
Hydrocephalus alone Spina bifda alone [congenital cleft of vertebral column] Anencephalus Hydrocephalus with spina bifda Meningocele Craniorthachischisis [congenital fissure of skull and spine] Microcephalus Encephalus Encephalucele Mongolism Idicoy, cretinism, glaucoma (1 each)	180 112 98 93 26 25 13 8 8 8 3	31.8 19.8 17.3 16.8 4.6 4.4 2.3 1.4 1.4

Potter and Adair (273, p. 101) call attention to the fact that onethird of the malformations that occur are of types often undiagnosed unless necropsy is performed; these defects include cardiac defects, gastrointestinal occlusions, diaphragmatic hernias, and kidney anomalies.

Diagnosis and treatment

The diagnosis of congenital malformations may be made in utero and in rare instances during birth, as well as after birth.

DIAGNOSIS BEFORE BIRTH

A tendency to vaginal bleeding in the early months of pregnancy is considered evidence of possible defects of the fetus. For this reason some obstetricians do not feel justified in attempting to prevent spontaneous abortion in certain cases. Later in pregnancy the occurrence of hydramnios is frequently associated with abnormal fetal development, especially anencephaly, a condition incompatible with life.

Roentgenograms of the pregnant woman's abdomen taken in the latter half of pregnancy may clarify the diagnosis of some types of fetal abnormality. Roentgenograms should always be made when there is a history of vaginal bleeding early in pregnancy or of previous births of congenitally defective infants, or when the uterus is enlarging out of proportion to the duration of pregnancy, as in cases of hydramnios.

DIAGNOSIS DURING BIRTH

Prolonged labor may be due to certain congenital defects in the infant, such as hydrocephalus or congenital cystic kidney, that obstruct passage through the birth canal. Diagnosis can usually be made by direct palpation.

DIAGNOSIS AFTER BIRTH

By far the greatest number of malformations are not apparent until birth, and some conditions may not be diagnosed then because of failure of the physician to make a careful examination or because of the nature of the defect. Cerebral and intraocular defects are often overlooked in the physician's examination and become apparent only after they begin to interfere with growth and development. Certain malformations of the heart ("congenital heart disease") may give no symptoms or signs until later in life (for diagnosis of heart malformations see p. 207), and frequently hemangiomata do not become visible in the skin until several days or weeks after birth.

The clinician's responsibility lies in the early diagnosis of malformations in living premature infants, with a view to correction at the time which offers the best prognosis. In some types of congenital defect correction, to be effective, must be made soon after birth; this is particularly true of tracheo-esophageal fistula, omphalocele, and occlusion at some point in the intestinal tract or of the rectal and anal openings. In other types, such as cleft palate, operation should be deferred, and in certain defects of the central nervous system operation may be deferred. Biliary-tract anomalies require time to make the differential diagnosis from catarrhal conditions causing temporary obstruction.

Since it is not practicable to discuss methods of diagnosis and correction for every type of congenital defect, the discussion will be limited to those conditions that there is most hope of correcting. The main points to bear in mind are: (1) that premature infants are believed to be especially likely to have congenital abnormalities; (2) that the abnormalities may not be apparent at birth; (3) that early diagnosis is important in giving a prognosis for survival and in planning specific treatment and general care; (4) that most of the laboratory tests for diagnosis can be applied to the premature infant, although special modifications of some of the tests may be necessary, and tests should be made with caution in consideration of the probable site of the lesion and the type of surgical correction that may be indicated; (5) that success in operations on premature infants calls for special skill and experience; and (6) that the infant must be given supportive treatment before the operation and, if necessary, during and after the operation.

For information in regard to choice of surgical methods and operative techniques, textbooks on surgery (such as 191 and 31) and current medical literature should be consulted.

The central nervous system

HYDROCEPHALUS

The diagnosis of hydrocephalus in its early stages is difficult because the premature infant's head appears large in relation to the infant's size. (See fig. 19). If large head-size is accompanied by spina bifida the diagnosis is obvious.

Evidences of hydrocephalus are:

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- 1. Head measurement above 33 cm.
- 2. Abnormal rate of increase of head circumference measured daily.
- Bulging, tense fontanelle.
 Separation of skull sutures.
 Vomiting.
 Convulsions.



Figure 19.—Hydrocephalus in a premature infant. Note marked disproportion between head and shoulders (courtesy Lewis K. Sweet, M. D., and John L. Parks, M. D., Washington, D. C.).



The condition must be differentiated from:

- 1. Normal megacephalus in a very premature infant.
- **2.** Meningitis. (See p. 274.)
- 3. Tetany. (See p. 330.)
- 4. Hemorrhage due to birth trauma. (See p. 227.)

Diagnostic aids

When the diagnosis of hydrocephalus is made, a lumbar puncture with examination of the spinal fluid for amount, pressure, cell count, presence or absence of blood (old or fresh), and culture will differentiate between increased intracranial tension due to simple hydrocephalus and that due to infections or intracranial hemorrhage.

The communicating type and the obstructive type (occlusion in the aqueduct of Sylvius) must also be differentiated. In the obstructive type, although signs of increased intracranial pressure are present, spinal fluid flows scantily on lumbar puncture. In these cases ventriculography will settle the diagnosis. As air injected into the lumbar subarachnoid space will usually enter the ventricles unless a block is present, stoppage of the air, revealed by roentgenograms, will help locate such a block.

Treatment

Congenital hydrocephalus is usually associated with spina bifida and meningocele, and correction of the hydrocephalus is dependent on correction of the spina bifida. When hydrocephalus is present at birth, surgical treatment, according to Holt and McIntosh (155, p. 996), is rarely successful.

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 and will not be discussed here. Spina bifida with myelomeningocele (nerve fibers in the sac) is more common than meningocele and has a more serious prognosis.

A malformation of the hindbrain termed the Arnold-Chiari malformation is related to low dorsal and lumbar myelomeningoceles. It consists in a downward elongation of the cerebellum and brain stem into the cervical portion of the bony spinal canal. The theory is that this condition is due to fixation of the cord at the site of the spina bifida. Other defects in the brain and skull (microgyria, craniolacunia, and so forth) are usually present and may be demonstrated in roentgenograms. "From the information at hand one must conclude that the combination of myelomeningocele, craniolacunia, microgyria, and Arnold-Chiari malformation constitutes a clinical entity. . . . The preoperative recognition of the syndrome is of great importance in planning a surgical attack on the problem (164)."

Both these types of spina bifida are usually accompanied by hydrocephalus, which may be present at birth or may develop shortly after birth. The commonest site of spina bifida is the lumbar region; 44 percent of the 462 cases reported by Ingraham and Swan (165) were in the lumbar region.

Treatment

Many reports of operative techniques for repair of spina bifida have been made, but on the whole the results have been discouraging or complete information has been lacking because of inadequate followup. Two reports with more favorable results are presented.

Penfield and Cone (256) reported in 1932 a new technique of operation in which the sac was collapsed and held so by fascial bands. They state that since the sac is preserved it continues to absorb cerebrospinal fluid and the operation does not increase the likelihood of hydrocephalus. They performed this operation in 19 cases of posterior cranium bifidum or spina bifida. There were no deaths. They give 4 case reports of infants operated on at ages varying from 12 hours to 1 month. Three of the infants were reexamined at $141/_{2}$ months, 2 years, and 7 years, respectively. The authors considered the results satisfactory in all 4 cases.

At the Children's Hospital in Boston the surgical technique calls for careful dissection of nerve fibers in the sac, which are returned to their position in the canal, excision of the sac, and tight closure of the dura, followed by "firm repair of the subcutaneous tissues and skin." Ingraham and Swan (165) say: "No attempt whatsoever is made to repair the bony defect." The surgical treatment of both spina bifida and cranium bifidum (see p. 195) is described in detail in the second article of the series, by Ingraham and Hamlin (163).

The present status of $4\overline{62}$ patients with spina bifida was reported by Ingraham and Swan (165) as follows. (It is not stated whether any of these infants were premature, but in a search of the records over a somewhat longer period only 5 infants weighing less than 5 lb. were found. Personal communication from J. K. Brines, M. D., Jan. 17, 1947.)

"There are 401 patients whose status is known and whose follow-up studies are considered adequate. Of these, 234 (58 percent) are alive. The remainder have died of a variety of causes. Operation was performed on 188, and 20 more are awaiting operation. Thus, 208 (52 percent) were or are thought to be suitable for operation. The immediate operative mortality in our hands was 12 percent.

"Of the patients who survived, 60 are considered normal and 61 are suffering from neurologic mild disability. The patients in both these groups may be considered as capable of leading a normal human existence. Thus, about 30 percent of the patients with spina bifida may look forward to a life unhampered by any significant incapacity resulting from their anomaly.

"Congenital lack of neural elements or destruction by long-standing compression results in neurodisability of an irreversible nature. One of these situations prevails, unfortunately, in the majority of cases where disability is present. However, occasionally local compression or traction on the cord is the cause of the progression of symptoms. If these are recognized, laminectomy offers promise of relief if the local situation permits operation. In our series there were 10 patients in whom relief or improvement in neurologic disability occurred following such an exploration.

"In the light of the data presented by this review, we believe that an outlook of extreme pessimism in the presence of spina bifida is unwarranted. Each patient must be evaluated as an individual problem." Ingraham and Swan (165) point out that "the presence of a mass constitutes an indication for operation in most cases . . . The age of choice for operations in infants is between 12 and 18 months. This allows time for the development and recognition of disabilities and hydrocephalus, for the local growth of skin adequate to permit closure, and for the child to develop in stature and nutrition into a better operative risk. However, certain local considerations may alter the desirability of waiting. If the sac is broken but uninfected, or if it is so thin as to threaten rupture at any moment, and the patient appears to be otherwise relatively normal, immediate operation is demanded to save his life. The presence of infection of the sac or of meningitis contra-indicates operation, but local dressings and chemotherapy may suffice to overcome the infection. . . .

"The presence of progressive hydrocephalus constitutes a contraindication to operation. Occasionally hydrocephalus stabilizes, and if this occurs, the contra-indication no longer exists.

"The presence of neurologic disability does **not** necessarily constitute a contra-indication; indeed, particularly in the older age group, if such disability is progressive, we believe that it is a strong argument for operation. In many of these patients, owing to their defect, the spinal cord becomes anchored at this site. As the child grows tension is placed on the cord, since it increases in length less rapidly than the vertebral canal. There may also be local compression by lipoid tumor growth. Both these elements contribute to the development of the signs of nerve dysfunction. This usually occurs between the ages of 6 and 10. In such cases the wisest procedure is exploratory laminectomy with a view to alleviating, if possible, the local situation. This attempt is occasionally successful."

Ingraham advises that when an infant is found to have an anomaly of the central nervous system, operative correction be undertaken at the most favorable time after consultation with a neurosurgeon. If this consultation must be held at a center distant from the birthplace, a case history and photographs of the infant showing the site and character of the defect should be forwarded by the physician requesting the consultation, prior to arrangements for operation. (Personal communication from F. D. Ingraham, M. D., Children's Hospital, Boston, June 1946.)

CRANIUM BIFIDUM

Cranium bifidum is a condition which is relatively rare compared with the spinal lesions. Ingraham and Swan (165) reported 84 cases, compared with 462 cases of spina bifida, and described the results of operation as follows: "In our series 59 patients had adequate follow-up studies. Of these, 52 underwent operation, and 17 (33 percent) of them subsequently died, either in the immediate postoperative period or at some later date. Twenty-one (34 percent) of the 59 patients are alive, well, and *entirely normal.*"

The gastrointestinal tract

Congenital abnormalities may result in partial or complete obstruction at certain points in the gastrointestinal tract (atresia or stenosis). The following clinical signs appear soon after birth (as soon as milk or water is given):

- 1. Vomiting.
- 2. Distention of abdomen.
- **3.** Abnormal meconium (no cornified epithelial cells or milk curds in smears).
- 4. Absence of fecal material or presence of a small amount combined with other symptoms of obstruction.
- 5. Dehydration fever.

The obstructing lesion may be located by roentgenograms of the abdomen *without* contrast media, which will show the intestinal pattern in the air-filled portion above the site of the obstruction. Ladd and Gross (191, p. 337) point out that it is unwise and in most cases unnecessary to give barium to infants with these abnormalities because it may clog the intestine and there is danger that the infant may aspirate it when vomiting. A small amount of a thin barium mixture may be given, however, if there is any question about the presence of obstruction.

Treatment in these cases depends on the site of the lesion and the type of anomaly. The operative techniques are similar to those used with older children.

THE ESOPHAGUS

There are a number of types of malformations of the esophagus, all of which are 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. The condition should be diagnosed soon after birth because of the 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 immediately corrected.

The diagnosis may be suspected, according to Ladd (190, p. 626), when the newborn infant has the following symptoms and signs:

- 1. Excess of saliva in the mouth and perhaps associated cyanosis.
- 2. Immediate vomiting after the first and any successive feeding.
- 3. Moist rales in the chest due to aspiration of fluids, most marked at right apex.
- 4. Abdomen distended with air and tympanitic or flat without tympany, depending on type of abnormality.

The diagnosis can and should be made at once by passing a catheter into the esophagus, which will meet with obstruction about 4 or 5 inches from the alveolus. Roentgenograms will show the end of the pouch by the position of the catheter without an opaque medium (which should not be given). If there is a tracheal fistula the film will show also that the stomach is distended with air.

Turner (358, p. 151) has made a plea for "more surgical courage" in the treatment of this otherwise hopeless condition. He gives 24 hours as the maximum time that should elapse before intervention. He stresses the importance of preliminary measures to correct dehydration and to improve the glycogen reserve of the body. and describes the operative procedure. Holinger (154) says in connection with this malformation: "Brilliant advances in thoracic surgery have permitted end-to-end anastomosis of the segments, with the result that many of these infants live and develop the ability to swallow normally." Ladd (190, p. 634) reports that of 34 infants operated on since 1939 according to the methods he outlines, 11 varying in age from 1¼ months to 4¼ years were living and generally doing well. Two of these infants were premature, weighing 4 lb. 6 oz. and 4 lb. 10 oz., respectively. One was admitted to the hospital at the age of 3 days and was doing well at the age of 2½ months; the other was admitted at the age of 2 days and was doing well at the age of 1¼ months. The important points are early diagnosis and immediate referral for skilled surgical treatment if the infant's life is to be saved.

CONGENITAL PYLORIC STENOSIS

No information has been found as to the incidence of pyloric stenosis among premature infants, though its occurrence in these infants has been reported (192, 107, 366). Rinvik (292) notes that in his series of 137 infants with pyloric stenosis 8 (5.8 percent) were premature. However, as about three-fourths of his series were above the average birth weight of Norwegian infants (3,500 gm. for males and 3,000 gm. for females) he believes that the figures "favor the conception that pyloric stenosis is particularly liable to occur among large infants." Wallgren (372) reported among 25,642 births in Göteborg, Sweden (1934-40), an incidence of hypertrophic pyloric stenosis of 0.4 percent; Davison (77), an incidence of 0.3 percent for the United Kingdom.

Males (80 to 85 percent) and first-born infants (50 to 60 percent) predominate in the reported series of infants with pyloric stenosis. The possibility of a hereditary factor is suggested, according to Ladd and his coworkers (192), by the familial occurrence of the abnormality, the fact that its occurrence in only one of two identical twins has not been reported, and its reported occurrence in stillbirths and in a 7-month fetus.

Symptoms of pyloric obstruction usually do not appear until the second or third week of life, and this has led to some doubt whether the condition is congenital in origin. Nelson (245) states, however, that there is little doubt of the congenital origin of this defect and that "on occasion, the anomaly has actually been demonstrated shortly after birth." The stenosis is due to thickening of the muscular coat of the pylorus, particularly of the circular fibers, and narrowing of the lumen.

The diagnosis, according to Nelson, can usually be made by a history of occasional vomiting, usually beginning about the second or third week of life and increasing until vomiting is projectile; constipation and loss of weight; visible reverse peristals (waves passing from the left side of the upper abdomen toward the pylorus); a palpable tumor, usually situated about midway between the umbilicus and the costal margin, just beyond the right rectus muscle. When the clinical diagnosis is in doubt roentgenograms after a barium meal will show gastric retention of the barium in the stomach with little or none in the duodenum. Caffey (59, p. 426) says that the normal emptying time for the stomach in the first 2 weeks of life may be as long as 8 hours and after the second week is usually about 5 hours. The condition must be differentiated from (1) duodenal obstruction, which is apparent a few hours after birth and in which the vomitus usually contains bile (if constriction is below the ampulla of Vater); and (2) so-called "pylorospasm," which is controlled by an antispasmodic or a sedative. With some infants vomiting occurs that suggests pyloric stenosis, but other diagnostic signs are lacking. It may be necessary to examine these infants roentgenologically to rule out an organic basis for the vomiting.

Treatment

Medical treatment

Administration of small feedings of milk thickened with cereal and antispasmodic or sedative treatment may be tried in these cases, but operation should be resorted to if definite improvement is not noted quickly. Rinvik (292, pp. 305, 314) reports favorable results in his clinic from medical treatment with eumydrine; since 1933, when the use of this drug was initiated, only 14 of 54 cases have been treated surgically. Szilagyi and McGraw (345, p. 784) say that eumydrine has been found to have "the full internal action of atropine with only onefiftieth of its toxicity. With its use remarkable results have been obtained." According to Nelson (245), however, the general opinion in many clinics in this country, including his own, is that operation should be performed as soon as the diagnosis is established. Ladd and his coworkers (192) believe that surgery as the treatment of choice is "almost the universal consensus."

Surgical treatment

Surgical treatment consists of pyloromyotomy, or the Frédet-Rammstedt operation in modified form. All aspects of the surgical handling of these cases, including preoperative and postoperative care, are described by Ladd and his coworkers (192). They have also reported the results of operation in 1,145 cases at the Children's Hospital in Boston since 1915. Operative mortality in 557 cases seen during the 10 years 1936-45 was 0.9 percent. In the last $3\frac{1}{2}$ years of this period 225 infants with pyloric stenosis were operated on consecutively without a fatality. No data are available on the number of premature infants in this series. (Personal communication from W. E. Ladd, M. D., Children's Hospital, Boston, June 1946.)

Three cases have been noted in which the Rammstedt operation was performed successfully on small premature infants at an early age. Gallagher (107) gives a case history of a Negro male infant who was operated on at the age of 33 days, when he weighed 3 lb. 83_4 oz.; when last seen, at the age of 2 years, he was in excellent health. This author says that Ladd in a personal communication told him of an infant who weighed 3 lb. 14 oz. when admitted to the hospital at the age of 12 days and was operated on 2 weeks later. Vickers and Conrad (366) report that they operated on an infant weighing 3 lb. 12 oz. at the age of 31 days.

Szilagyi and McGraw (345) have published a comprehensive review of the medical literature on congenital pyloric stenosis and a clinical analysis of their own series of 34 cases, together with an extensive bibliography. They conclude (p. 807) in regard to treatment:

"The disease is easily curable by medical means in its mild form; manageable, but at prohibitive expense of time, energy, and money, by medical means in most of its more severe forms; it is easily curable in all its grades by surgical means. Medical treatment should be restricted to mild cases but should be given a trial in all but the most severe cases.

"Adequate preparation of the patient before operation is a factor as important as the skill of the surgeon, or perhaps more so. The Frédet-Rammstedt operation, or pyloromyotomy, has no equal among the other surgical procedures proposed."

THE INTESTINAL TRACT

Types of malformation

The development of the intestines is a very complicated process. The various congenital abnormalities of the intestinal tract are due to arrest of development in fetal life or to persistence of fetal structures. 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 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, and then a solid cord in which a lumen gradually develops by vacuolization.

The main types of malformations are atresia, stenosis, malrotation, and Meckel's diverticulum (persistence of the omphalomesenteric duct). Atresia and stenosis are the commonest of these conditions to give rise to symptoms of obstruction in the neonatal period.

Atresia and stenosis of the intestines, according to Ladd and Gross (191, p. 25) are due to "arrest in development during the second or third month of fetal life."

Atresia

Atresia is due to persistence of one or more of the septa (between vacuolized areas) resulting in obstruction by an internal diaphragm or by ending of the intestine in a blind pouch. The anomaly may be single or multiple.

In the series of 52 cases reported by Ladd and Gross (p. 41) the ileum was by far the most frequent site of atresia.

Obviously if completely obstructive lesions are unrecognized and untreated death is inevitable. The mortality rate is high even in cases in which operation is performed under advantageous circumstances early diagnosis, preoperative treatment, and the best operative technique known. Ladd and Gross had only 7 recoveries in 52 infants operated on. Associated anomalies and postoperative infections played major roles in causing death. With earlier diagnosis, according to Ladd and Gross (**p. 34**), surgical treatment "is meeting with increasing success," and with the advent of chemotherapy deaths from peritonitis and pneumonia should be reduced. (For discussion of the operative techniques for various types of atresia see Ladd and Gross, **191, pp. 35-40.**)

Stenosis

Stenosis is due to incomplete reduction of the solid stage of the intestine in fetal development. Stenosis is more common in the duodenum than in any other part of the intestine, but it may be present at any level in the small or large intestine. Symptoms of obstruction are commonest in the neonatal period but may appear in later infancy or childhood.

The results of operation for stenosis are better than for atresia, and the prognosis is most favorable when the stenosis is high up in the intestinal tract. Among the 22 infants and children operated on at Children's Hospital, Boston, and reported by Ladd and Gross (p. 51)10 recovered. Among the 11 cases in which the stenosis was in the duodenum there were 7 recoveries.

Malrotation

In the experience of Ladd and Gross (p. 53) the obstruction (volvulus) that is due to "improper rotation" is high up in the intestine, resulting frequently from pressure on the second and third portions of the duodenum.

McIntosh and Donovan (225) give 20 case reports of intestinal obstruction due to "errors of rotation." Included among the 18 cases operated on were 12 infants 1 month old or less. Of those whose weight was given the smallest infants operated on weighed 2,250 gm. (at 15 days), 2,430 gm. (at 7 days), and 2,560 gm. (at 29 days). The smallest of these three infants died; the other two survived. Among the 12 infants 1 month of age or under there were 8 survivals and 4 deaths. The authors stress the fact (*p. 166*) that an anomaly of rotation must be considered as a possible cause in all cases of acute or chronic obstruction, particularly duodenal obstruction.

Meckel's diverticulum (persistence of omphalomesenteric duct)

Meckel's diverticulum is a pouch connected with the intestine (the ileum) at one end and with the umbilicus at the other by a cord (the remains of a fetal structure, the primitive yolk stalk) which should have lost its connection with the intestine before the infant was born. Symptoms of obstruction due to this anomaly may occur at any age. In the series of cases reported by Ladd and Gross (191, p. 76) approximately one-half came to the hospital within the first 2 years of life. The youngest was 5 hours old.

Hemorrhage from the bowel is one of the symptoms associated with Meckel's diverticulum, in addition to those of obstruction. The bleeding is due to ulceration at or near the site of the sac. Of 73 infants and children operated on for Meckel's diverticulum at the Children's Hospital, Boston (191, p. 81), 57 "recovered." The ages were not stated.

Symptoms

The outstanding symptom of any of these conditions is persistent vomiting. Other symptoms are dependent on where the obstruction is and whether it is partial or complete. Immediate diagnosis of intestinal obstruction and appropriate medical and surgical treatment are essential to save the infant's life.

Diagnosis

Clinical signs

The vomiting must be differentiated from that due to esophageal and pyloric lesions and to strangulated inguinal hernia. If bile is present in the vomitus the obstruction is below the ampulla of Vater. If the obstruction is in the lower ileum or the colon fecal material will eventually be vomited. Fecal material may be passed through the bowel in small amounts or not at all, depending on the extent of the obstruction, but meconium may be passed even if the obstruction is The character of the meconium is an important diagnostic complete. aid. If, on microscopic examination, no cornified epithelial cells are found, the obstruction is known to be complete because swallowed amniotic fluid, which contains these cells, has evidently not been able to get past (Farber's test). Other clinical diagnostic points that aid in locating obstructions are discussed in detail by Ladd and Gross. These authors consider (p. 29) that "if these babies are carefully observed during the first 24 or 48 hours of life, the clinical findings are usually sufficient to make a correct diagnosis."

Roentgenograms

In general, however, an infant who has early and persistent vomiting should be subjected to roentgen diagnosis without delay, with the double object of confirming the clinical diagnosis and helping to locate the obstruction. Ladd and Gross (p. 30) point out that "films of the abdomen, without the use of contrast media, will give all the important information in most cases." Anteroposterior and lateral exposures should be made with the infant in both head-up and head-down positions. Air-, gas-, or fluid-filled portions of the intestines above the obstruction will thereby be differentiated from the unfilled portions below the obstruction.

Ladd and Gross caution against the use of barium by mouth because the barium may clog the intestinal tract or be aspirated during vomiting. If used, it should be a thin mixture and should be removed from the stomach by lavage immediately after the examination, according to these authors. If colonic obstruction is suspected and a barium meal has been decided upon, a barium enema should be given first, according to Caffey (59, p. 459), to visualize the colon and the caecum. Ladd and Gross, however, believe the barium enema, as well as the barium meal, to be undesirable unless the abdomen has been decompressed by ileostomy, in which case a barium enema causes no distress to the infant and may give valuable information as to the size and continuity of the colon.

Under conditions, especially on the first day of life, in which roentgenograms without contrast media have been taken but do not definitely locate the obstruction, Mellins and Milman (229), to avoid giving barium, have recently advocated injection of air into the stomach to heighten the contrast in the pictures of the intestines above and the intestines below the obstruction. The gastric contents are aspirated and 60 to 90 cc. of air is introduced slowly under fluoroscopic control while the infant is rotated to the left to visualize the duodenum. The air is then aspirated and the tube withdrawn. Complete and partial obstruction can be differentiated by serial roentgenograms at hourly intervals.

Treatment

If the roentgenograms and the clinical course combine to suggest strongly a diagnosis of intestinal obstruction, operation should be undertaken without further attempt to locate the obstruction. Preoperative medical treatment to combat dehydration, prevent hemorrhage, and conserve the infant's body heat during operation are of great importance.

The results of operations to relieve intestinal obstruction have been given in the general discussion of the various types of defects. The following history shows that it is possible to operate successfully on a premature infant even when more than one intestinal anomaly is present. Duncan and his associates (88), in presenting this case, believed it to record the first successful surgical treatment of multiple atresias of the small intestine.

A white male born one month prematurely, weight 2,041 gm. (4 lb. 8 oz.), was hospitalized at 36 hours with a diagnosis of congenital intestinal obstruction. He had vomited everything given by mouth from birth and had no stools. The vomitus was bilestained and the infant jaundiced.

Fluoroscopic and roentgenographic examination showed moderate gaseous distention of stomach and duodenum, which ended in the region of the duodenojejunal flexure. The rest of the alimentary tract showed no gas. Parenteral fluid and vitamin **K** were given, and the stomach was lavaged prior to operation. At operation the jejunum was found to end blindly about 10 cm. below the ligament of Treitz; then came an isolated loop of bowel about 4 cm. long; then a section of bowel 17 cm. long, ending blindly at both ends. In it was a small perforation. The isolated sections of bowel had separate mesenteries. "At the proximal end of the remaining loops of small intestine there were two areas of stenosis."

The small, isolated loop was left undisturbed; the larger blind loop was resected; the proximal end of the distal small intestine, containing two areas of stenosis, was resected because the mesentery was torn during operation. A side-to-side anastomosis was made between the distal intestinal stump and the proximal dilated jejunum. In spite of a prolonged period of biliary obstruction and two episodes of severe diarrhea complicating the postoperative course the infant survived. When last seen at the age of 10 months he was in "excellent health" and weighed 8.2 kg. (18 lb.).

THE ANUS AND RECTUM

Atresia or stenosis of the anus or rectum is a relatively uncommon malformation, estimates of incidence being given as 1 in 5,000 and 1 in 8,000 infants born. The various types are described by Ladd and Gross (191, p. 169). The condition may be complicated by fistulous connection with the genitourinary system or the perineum (27). (See fig. 20.)

Symptoms

Symptoms depend on the type of malformation. In the second and third types (shown in figure 20) symptoms of acute obstruction are apparent from birth unless fistulas are present.



(a) Types of anal and rectal abnormalities.

Type 1. Stenosis at anus or at a point several centimeters above the anus.

Type 2. Imperforate anus; obstruction due to persistent membrane. Type 3. Imperforate anus; rectal pouch ending blindly some distance above anus.

Type 4. Anus and anal pouch normal; rectal pouch ends blindly in hollow of sacrum.



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RECTOPERINEAL

RECTOPERINEAL RECTOVESICAL RECTOURETHRAL (b) Types of fistulas encountered in 48 male patients.

RECTOVESICAL &

RECTOVAGINAL

(c) Types of fistulas encountered in 70 female patients.

Figure 20.—Anal and rectal malformations (from Ladd, William E.; and Gross, Robert E.: Abdominal Surgery of Infancy and Childhood. Phila.: Saunders, 1941).

RECTOVAGINAL

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Diagnosis

The diagnosis may be made by (1) direct inspection, if there is no anal opening or an abnormal perineal opening; (2) by roentgeno-graphic examination (method of Wangensteen and Rice). The The exposure is made with the infant held by the heels. When he is in this position the gas in the intestine rises and the rectal pouch is outlined. Ladd and Gross (p. 176) point out that if this test is made during the first 24 hours the absence of gas in the rectum due to obstruction by meconium in the lower intestine may lead to error in diagnosis.

These authors call attention to the high incidence (28 percent) of associated congenital anomalies in their series of 214 cases.

Treatment

Treatment of rectal and anal abnormalities depends upon the type of anomaly. Ladd and Gross (p. 186) report a mortality in the Children's Hospital series of 26 percent-8 percent in cases of type 1; 11 percent in type 2; 26 percent in type 3; and 57 percent in type 4. (See The authors comment: "The lower fistulas (rectoperineal fig. 20.) and rectovaginal) are relatively easy to close when the rectal obstruction is corrected in the first few days of life. The higher fistulas (rectourethral and rectovesical), however, are very difficult to reach through a perineal incision in a newborn infant; hence it is found best to delay treatment of such communications until the patient attains an age of 6 to 9 years."

THE BILIARY TRACT

There are a large number of abnormalities of development of the biliary tract which result in obstruction to the flow of bile into the intestine. In certain types of atresia it is possible to anastomose remnants of the bile ducts with adjacent portions of the intestine. Ladd and Gross (191, p. 260) state that "the number of such successful operations is small, but in a condition which is otherwise uniformly fatal, it is best to explore all of these babies in the hope of finding a condition which is amenable to surgical relief." The various types of atresia of the extrahepatic duct are shown in figure 21.



Figure 21.—Sketch of types of atresia of the extrahepatic bile ducts as found in surgical exploration of 45 cases (from Ladd, William E.; and Gross, Robert E.: Abdominal Surgery of Infancy and Childhood. Phila.: Saun-ders, 1941).
1. Hepatic duct patent and connecting with liver.

2. Hepatic and part of common duct patent (gallbladder may be atretic or patent).

3. Hepatic duct atretic; gallbladder, cystic duct and common duct normal. 4. Hepatic and common ducts atretic,
Symptoms 5 1

1

The outstanding symptom is jaundice, which is usually present at birth or shortly after and which becomes increasingly severe and is persistent. The stools are clay-colored or white from birth, and the urine is bile-stained. The liver usually becomes much enlarged and the spleen may be slightly enlarged. There may be a tendency to hemorrhage. The icteric index (see p. 288) is elevated (284).

Diagnosis

Differential diagnosis must be made from:

- 1. Icterus neonatorum, which tends to diminish rapidly after about the tenth day. The infant is symptom-free.
- 2. Erythroblastosis. Blood shows large and increasing quantities of nucleated erythrocytes; splenomegaly is common; there is Rh incompatibility of the blood of mother and infant.
- 3. Sepsis, shown by fever, leucocytosis, or progressive anemia and positive blood culture.
- 4. Congenital syphilis, by means of maternal history, blood Wassermann of mother and infant, and roentgenograms of the long bones.
- 5. Inspissated bile or mucus causing obstruction, which is very difficult to differentiate from the atresias. Variation in the intensity of jaundice and intermittent appearance of bile in the stools are evidences that the obstruction is probably not due to congenital causes, but this intermittency is not always shown.

Treatment

As has been pointed out, the differential diagnosis between obstruction of the bile ducts by mucus or inspissated bile and by congenital abnormalities is sometimes difficult. Obstruction by mucus or bile, much the rarer condition, may clear up as a result of medical treatment but is more likely to require surgical treatment. Medical treatment should be symptomatic with low-fat diet and careful attention to the infant's nutrition and fluid requirements. Ladd and Gross (191, pp. 275, 277) report one case in which injection, by duodenal tube, of 25percent magnesium-sulfate solution stimulated the flow of bile sufficiently to dislodge the obstruction, but this treatment failed in other cases. Eight infants were given surgical treatment consisting of exploration of the extrabiliary system with manipulation of the system or with irrigation of the ducts by way of the gall bladder; six of these infants survived and had no recurrence of symptoms.

Congenital abnormalities, which are much more common, may or may not be amenable to surgical correction depending on the type of anomaly. At the Children's Hospital in Boston surgical exploration has been done since 1916 in all cases except a few that were at once judged inoperable. Ladd and Gross (p.266) state that delay in operating until the infant is 4 to 6 weeks old is an advantage provided the infant's condition warrants it, because delay allows time to make an exact diagnosis. Further delay, however, adds nothing to the diagnostic evidence and involves the danger that the infant may develop an infection or anemia.

Premature Infants

Operative procedures depend on the site of the anomaly. In the Children's Hospital series reported by Ladd and Gross of 45 cases of atresia of the biliary tract in which exploration was done, 9 cases were found to be operable; that is, the hepatic duct was patent or the common duct was connected with the intrahepatic duct system but not with the duodenum. The operation consisted in anastomosis of the biliary tract with the intestinal tract. The types of operation and the results are shown in table 50. The 3 infants who were judged in-operable after exploration died at an average age of 5 months.

 TABLE 50
 Results of treatment in operable cases of atresia of extrabiliary system— Children's Hospital series (Ladd and Gross)

Treatment	Infants died	Infants recovered
Total	3	6
A tresia of lower end of hepatic duct (hepaticoduodenostomy) A tresia of lower end of common duct: Choledochoduodenostomy		2
Cholecystoduodenostomy Cholecystostomy	1	1

The six children who survived had been followed for 4 to 12 years and were reported to have been in excellent general health.

The respiratory tract

Various types of malformations of the trachea occur, all of which are rare. The commonest of them is tracheo-esophageal fistula. (For a discussion of the diagnosis and treatment of this condition, see p. 196.)

Bronchus abnormalities occur in connection with maldevelopment of the lungs.

Congenital abnormalities of the lungs are very rare. Occasionally unilateral aplasia or hypoplasia, complete or partial, occurs. Caffey (59, p. 229) points out the frequency of association of this condition with other anomalies, especially vertebral anomalies. There is hypertrophy of the normally developed lung and displacement of the heart. The condition is not incompatible with life.

Caffey states that "a conclusive roentgen diagnosis cannot be made on the basis of conventional films; therefore bronchographic or bronchoscopic observations are necessary to demonstrate that a primary bronchus, usually the right, is absent." In cases of partial hypoplasia a portion of the hypoplastic lung is visible.

Congenital cysts of the lung occur but are extremely rare.

The cardiovascular system

There are many types of malformations involving one or more parts of the heart and of the great vessels which may occur alone or in combination. Malformation may be of such a nature that no symptoms are produced; or, if symptoms are present, they may be occasional or constant, mild or severe.

SYMPTOMS AND DIAGNOSIS

Although it is important to diagnose the exact type of anomaly from the point of view of prognosis and treatment, the physician who has not had special training and experience will usually have difficulty in interpreting clinical signs and roentgenograms in young infants. For example, in the early neonatal period precordial murmurs are frequently heard, but in the largest proportion of cases they have no pathologic significance and are probably the result of delayed closure of one of the fetal openings—the foramen ovale or the ductus arteriosus. On the other hand, there may be a gross defect in one of the fetal structures without any audible murmur. In regard to roentgenograms, Caffey (59, p. 374) states: "During the first weeks and months of life, relatively little information can be gained regarding the exact structure and the extent of many of the cardiac malformations."

The diagnosis of congenital cardiac anomalies in an infant perhaps can best be made on the "functional" basis; that is, on the presence or absence of symptoms and signs of circulatory disturbance and, if present, on their degree and persistence. The commonest symptom is cyanosis. (For causes of cyanosis in the neonatal period see p. 109.) Abbott (1, p. 228) has suggested a classification of cardiac anomalies into three groups: (1) acyanotic (no abnormal arteriovenous blood mixture); (2) potentially cyanotic (arteriovenous shunt from left to right that would cause cyanosis if the flow were reversed); (3) cyanotic (right-sided valvular lesions, with fetal passages closed, or permanent venous-arterial shunt). Other signs of circulatory embarrassment may be present or may appear later, such as rapid or labored respiration, liver enlargement, and edema. Clubbing of fingers and toes is later common in the cyanotic group. Except in the presence of very severe defects these signs do not appear until the infant's activities increase. In later infancy and in childhood physical growth may be The differential diagnosis of the types of cardiac anomalies, retarded. which may occur alone or in various combinations, will not be dis-cussed. Caffey (59, p. 374 ff.) discusses roentgenographic diagnosis in detail.

TREATMENT

In infancy there is no specific medical treatment for any one of these anomalies. Cyanosis and respiratory embarrassment can be relieved temporarily by administration of oxygen, and the cardiac muscle can be bolstered by the use of digitalis, as in any case of cardiac decompensation. There are, however, two types of cardiac anomalies that are amenable to surgical treatment in late infancy or early childhood—patent ductus arteriosus and the tetralogy of Fallot. Surgical techniques are being developed that may make it possible to alleviate symptoms due to coarctation of the aorta also.

Gross (129, 130, 131) has developed methods for closure of a patent ductus arteriosus. In his series of 90 surgically treated cases there have been 4 surgical deaths, a rate of 4.4 percent. "The vast majority of patients who have survived operation have obtained an extremely gratifying result. . . At first all of the subjects chosen for operation were in the childhood years. However, the age limit has been gradually diminished, and in one baby 11 months of age the operation has been successful (131)."

Premature Infants

The diagnosis and treatment of the tetralogy of Fallot (dextroposition of the aorta, pulmonary stenosis, interventricular septal defect, and hypertrophy of the right ventricle) have been described by Blalock and Taussig (40). Blalock (39, p. 69) reported that up to November 1, 1945, 57 operations had been done on 55 patients with the diagnosis of tetralogy of Fallot. Of these, 40 showed definite improvement. "The condition of most of the children has been altered from almost total invalidism to apparent, if not real, normality." Blalock points out that since the diagnosis is more difficult to make in infants than in older children and infants do not withstand the operation so well, surgery is not recommended for children under 18 months of age unless their chances of survival are poor. In his series one infant was operated on at the age of 8 months and his condition improved. Another case (40) was a premature infant (birth weight, 1,105 gm.), who was operated on at the age of about 15 months. She showed striking clinical improvement after the operation, but it was thought that another operation might be necessary because the cyanosis did not completely disappear.

Potts, Smith, and Gibson (276, p. 631) reported more recently that after experimentation with animals they had operated by a different method on 3 children (aged, respectively, 21 months, 11 years, and 7 years) whose condition was diagnosed as the tetralogy of Fallot. The infant and the 7-year-old child survived the operation and were reported to have been "tremendously benefited."

(For discussion of congenital defects of the heart in infants whose mothers had rubella early in pregnancy see p. 184.)

The urinary tract

Malformations of the urinary tract are very common and occur much more frequently in male than in female infants. The frequency with which these malformations occur is related to the very complicated developmental process of the genitourinary system, particularly in the male.

Bigler (35, p. 1), in a discussion of the embryology of the urinary tract, points out that the urinary and genital tracts have a common origin and are closely associated and interrelated. "During the development of the urinary system both progressive and degenerative changes take place through a succession of three organs, the pronephros, the mesonephros, and finally the metanephros." The last becomes the permanent kidney.

During the developmental period the blood supply to various parts is established, budding and branching of ducts and tubules take place to form new structures, proper joining of parts is established, and changes in the position of the kidney occur. By the sixth month the kidney is a lobulated organ with thick cortex and medulla but small pelvis.

There are a large number of anomalies that result from interruption of the normal course of development, among which are agenesis, aplasia or hypoplasia, duplication of parts, obstructions due to persistence of fetal conditions, malposition, malrotation, abnormal openings of ducts, and other abnormal conditions such as cysts and diverticula. (See fig. 22.)

Congenital Malformations

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Figure 22.—Schematic drawing of the urinary tract showing locations and types of the common congenital anomalies. Adapted from Helmholz and Amberg (from Bigler, J. A.: Anomalies of the Urinary Tract in I. Mc-Quarrie (ed.): Brennemann's Practice of Pediatrics. Vol. III. Hagerstown, Md.: Prior, 1948).

Holt and McIntosh (155, p. 805) state that many of the malformations of the genitourinary tract "are of little clinical interest and produce no symptoms throughout life. With almost any type, however, the susceptibility to stone formation, infection, and degenerative disease is definitely increased. Two groups only are by themselves of clinical importance—congenital cystic kidneys and malformations causing urinary obstruction."

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MALFORMATIONS OF THE KIDNEY

Congenital cystic kidney

The commonest kidney malformation is a congenital cystic condition the cause of which has not been determined. The occurrence of a few small cysts in the kidneys is a relatively frequent finding and has no clinical significance. When the cysts are small but widespread or one or more large cysts occur, obviously kidney function will be impaired. The condition may be found in one kidney, but more frequently both kidneys are affected. In 12,080 autopsies on children under 15 years of age Campbell (60, p. 206) found 48 cases of congenital polycystic renal disease; 42 were infants under 1 year.

Unless one or both kidneys are greatly enlarged and irregularities of the contour are palpable, the condition is usually overlooked during the neonatal period; symptoms of renal insufficiency or secondary infection of the urinary tract appear later. It should be pointed out that the kidneys in newborn infants, both term and premature, are usually easily palpable, the left more so than the right, since it is normally lower.



Figure 23.—Polycystic kidney, showing the stretched "spider" pelvis with elongation and stenosis of the primary and secondary calices (from Caffey, John: Pediatric X-Ray Diagnosis. Chicago: Yearbook Publishers, [1945]). The diagnosis of cystic kidneys can be demonstrated in pyelograms

which show the characteristic "spider" pelvis. (See fig. 23.) The prognosis is poor, according to Campbell (60, p. 206). Ac-cording to Holt and McIntosh (155, p. 805), "the disease is not amenable to treatment."

Hydronephrosis

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Hydronephrosis is usually associated with uretero-pelvic obstruction, but may occur without blockage, as a result of faulty muscular development and innervation. The condition is usually discovered postmortem, but the diagnosis of urinary-tract infection may lead to antemortem diagnosis of hydronephrosis also. If one of the kidneys is adequate, the condition is compatible with life. The diagnosis is made by pyelography.

OTHER MALFORMATIONS OF THE URINARY TRACT

The commonest types of malformations that obstruct urine flow and result in kidney damage will be discussed briefly. (For complete discussion of all types of anomalies and their diagnosis and treatment. textbooks must be consulted. See 60 and 179.)

The ureters

The ureters are the ducts of the kidney and develop as buds from the Wolffian ducts. They extend first as cords and then as hollow tubes from the uretero-pelvic junction to the vesical trigone. Their length is related to trunk length in the ration of 1:2. The process of development of the ureters is so complicated that arrest of development or maldevelopment is frequent.

According to Campbell (60, p. 188), in a series of 12,080 autopsies of children under 15, the commonest anomalies of the urinary tract were idiopathic dilatation of the ureter and stricture. In a series of 109 cases of congenital lesions of the urinary tract found clinically and postmortem, reported by Bigler (35, p. 15) from the Children's Memorial Hospital, Chicago, the following anomalies of the ureters were found:

Obstruction at pelvi-ureteral junction, 17 cases.

Obstruction in the course of the ureter, 1 case.

Obstruction in the vesico-ureteral region, 22 cases.

The diagnosis of the site of the anomaly and the treatment are in the field of the genitourinary specialists. With a small premature infant both the diagnosis and the treatment are especially difficult.

The urethra

Obstruction of the urethra occurs in male infants, most commonly at the upper end, from the presence of membranous folds, the so-called posterior urethral valves, which opening inward, obstruct the outward flow of urine (410, p. 509). Obstruction may also be due in rare instances to congenital narrowing of the urethra or to the presence of a degree of phimosis that occludes the urethral orifice.

Symptoms are failure to void or voiding of small amounts of urine. The urinary bladder becomes greatly distended. The diagnosis of phimosis is obvious on inspection, and the anomaly is easily corrected by circumcision. In cases of urethral constriction and of posterior urethral valves the diagnosis presents some difficulty. In the former condition there is obstruction to passage of a catheter; in the latter no obstruction is met when the catheter is introduced into the bladder because it holds the valves open. The diagnosis of congenital valves can be made definite by a cystogram.

Removal of the values is a highly specialized surgical procedure. The prognosis is usually grave, according to Campbell (60, p. 349); but after bladder drainage, if the condition of the patient is otherwise satisfactory, "operation may be performed with relative safety."

The bladder

Malformations of the bladder are relatively rare. Among them are persistence of the urachus, diverticula, and exstrophy of the bladder.

Patency of the urachus—due to failure of the allantoic canal between the umbilicus and the bladder to be obliterated—is important from the clincipal standpoint only when cysts are formed or when urine is discharged at the abdominal end. In the latter case the lower urinary tract is usually obstructed. Except in cases in which the canal is closed at both ends, the lesion can be visualized in roentgenograms by injection of an opaque medium into the bladder or at the umbilicus. Operative removal and repair are possible but may be complicated if the cyst or sinus has become infected.

Diverticula of the bladder, which occur much more commonly in males than in females, are usually associated with obstruction at the bladder outlet or in the urethra. They may exist without symptoms, however, and be discovered in later life in cystoscopic examination made for other reasons. The lesion has been found in the fetus and newborn infant (59, p. 520). Kretschmer (188) reported 25 cases in children (19 from other studies and 6 of his own); there were 6 cases in infants under 1 year.

Since symptoms, if present, usually point obviously to the urinary tract, the tract should be given a complete examination including urinalysis, cystoscopy, and cystograms. In the 6 cases listed by Kretschmer the diagnosis was made clinically or by cystoscopic or roentgenographic examination in 2 cases, at autopsy in 3 (including 1 infant who had previously had an intravenous pyelogram), and at operation in 1.

Exstrophy of the bladder is obvious on inspection. It is much more frequent in males than in females. Campbell (60, p. 304) describes it as "an absence of the anterior vesical and lower abdominal walls with eversion of the posterior bladder wall. . . . The ureteral orifices are usually easily found and freely discharge the urine externally." The lesion may be incomplete (a slight defect in the abdominal wall, slight protrusion of the bladder, pubes united, and genitals normal) or complete (protrusion of posterior bladder wall, separation of pubes, and epispadias). Incomplete exstrophy is rare and is readily cured by plastic closure of the bladder and the abdominal wall. Complete exstrophy is the usual finding. The only treatment is ureteral transplantation to the rectum. The prognosis is poor at all ages.

The eye

Among the numerous malformations of the eye only four will be discussed: congenital cataract, retinoblastoma, ptosis of the eyelid, and strabismus. Congenital cataract and retinoblastoma must be differentiated from retrolental fibroplasia, which is rare except in premature infants and is discussed on pages 336–338.

CONGENITAL CATARACT

Congenital cataract may be apparent at birth or may not become apparent until some time during infancy or even in childhood. Recently a frequent association has been shown between this condition and maternal rubella in early pregnancy. (See p. 184.)

The most important type of developmental cataract in children, according to Lillie (210, p. 1297), is zonular cataract, which he describes as follows: "It is almost always bilateral and usually symmetrical. The opacity of the lens is evident with focal illumination as a pearly-gray, round area in the center of the lens with concentric alternating rings of clear and translucent lens substance around it. Frequently the peripheral translucent area is capped by a few radially situated opaque spokes, or 'riders.' Ophthalmoscopically the opaque area is black against the red reflex of the fundus. This cataract is most dense at the margin of the disk."

For confirmation of the diagnosis of congenital cataract and for therapy an ophthalmologist should be consulted. Walsh (373, p. 336) points out that at Johns Hopkins Hospital operation is never attempted before the infant is 6 months of age and as a rule not until he is 10 to 12 months old. He believes that bilateral ocular operations are permissible in order to avoid repetition of a general anesthetic, but he adds: "Cautious operators, however, rarely operate on both eyes at the same time." After discussing the various types and methods of operation he states: "In total cataracts there is no question as to the desirability of operation, but partial and stationary cataracts present nice problems of judgment."

RETINOBLASTOMA

Retinoblastoma is a condition described by Lillie as "a relatively rare, malignant tumor which occurs almost exclusively in infants and young children. It presumably has its onset in utero, and in many instances a familial pattern can be demonstrated." The tumor, which is usually unilateral, appears at first as a "small, round, yellowish-white nodule," but it soon spreads on the retina or into the vitreous. It may be 6 to 12 months, according to Lillie (210, p. 1306), before the tumor produces such clinical manifestations as dilatation of the pupil, yellow reflex of the pupil, and defective vision. The tumor extends by way of the optic nerve and then involves the central nervous system.

Differential diagnosis must be made from a variety of conditions. In premature infants retinoblastoma must be differentiated from "persistent posterior fibrovascular sheath of the lens." (See Retrolental Fibroplasia, p. 336.)

The treatment of retinoblastoma, as given by Lillie, is "early enucleation of the involved eye with removal of the largest possible portion of the optic nerve. Whether or not infiltration is present in sections of the severed end of the optic nerve determines the prognosis. Local recurrences may develop within 4 to 12 months."

PTOSIS OF THE EYELIDS AND STRABISMUS

Ptosis of the eyelids and strabismus may be congenital in origin or may be the result of birth trauma. According to Walsh (373, p. 328), ptosis of the eyelids is frequently observed in newborn infants but usually disappears within a few days. "When it fails to improve, however, it may be due to a defect in development or absence of the levator," and in this case operation is usually indicated.

Congenital strabismus (squint) is also commonly seen in the early neonatal period. Walsh points out that a true squint (permanent) must be differentiated from the spurious squint (transient) that is frequently seen in the early neonatal period. According to Walsh, the spurious squint may be evident up to the third month when coordinate movements of the eyes are usually established. He says: "The upper limit at which incoordinate movements are noted is 8 months of age for vertical movements and 18 months for lateral movements. True squint can frequently be recognized from birth onward by the fact that one or both eyes consistently deviate in some particular direction."

The treatment of true squint consists in muscle training. Operative correction may be necessary in some cases. The infant should be under the care of an ophthalmologist.

Hernias

Premature infants are prone to hernias, especially umbilical hernia. Ylppö (409, p. 497) found that premature infants were more frequently subject to hernia than full-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. In umbilical hernia an impulse can be felt when the infant cries, and the hernia can be reduced when the infant is quiet.

The consensus of opinion is that strapping of the hernia with adhesive tape is unnecessary and that spontaneous reduction occurs in a large proportion of cases. If the hernia increases in size and there is danger of infection, operation may be indicated.

UMBILICAL EVENTRATION

Umbilical eventration (omphalocele) is obvious at birth. The sac may contain intestinal loops only or other abdominal viscera. This anomaly thus represents persistence of the fetal condition that exists prior to the tenth week of intrauterine life. According to Ladd and Gross (191, p. 315), there is no alternative but radical and immediate operation. "The surgical repair should be performed on the first day and preferably within the first few hours. Indeed it has been aptly said that the baby should pass from the obstetrician's hands onto the operating table."

INGUINAL HERNIA

Inguinal hernias must be differentiated from hydrocele; both are relatively common in premature infants. Table 51 shows the incidence of inguinal hernia by birth-weight groups, as reported by Rambar and Goldberg (281).

. Weight (gm.)	Total number of infants	Total number of hernias	Percent who de- veloped hernia	
Less than 1,000	9	2	22. 22	
	107	5	4. 67	
	339	11	3. 25	
	324	18	5. 25	
	51	2	3. 92	

TABLE 51 Relationship of inguinal hernia to birth weight (Rambar and Goldberg)

Treatment is palliative. Hess (147) advises the use of a yarn truss or a specially designed cotton bandage. Strangulation may occur and operation has been successfully performed on premature infants.

DIAPHRAGMATIC HERNIA

Herniation of the intestines and other abdominal viscera through the diaphragm into the thoracic cavity may occur through one of the pleuro-peritoneal hiatuses or the foramen of Morgagni. These points represent developmental defects in the complicated mechanism by which the thoracic and abdominal cavities are connected in embryonic life. (See fig. 24.)



Figure 24.—Schematic representation of the normal openings and the pathologic congenital defects in the diaphragm as seen from above (from Caffey, John: Pediatric X-Ray Diagnosis. Chicago: Yearbook Publishers, [1945]).

Ladd and Gross (191, p. 333) state: "Diaphragmatic hernia is a not uncommon lesion in the newly born. It can be easily detected by physical examination and roentgenologic study. It can be satisfactorily and permanently cured by properly executed surgical procedures. The recovery of 11 of the last 13 patients we have treated indi-770895-48-15

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cates that diaphragmatic defects can be successfully repaired in babies in spite of the previously reported high mortality rates.

"An extensive literature has accumulated on the general subject of diaphragmatic hernia, but relatively little attention has been paid to the condition as it occurs in the first few weeks or months of life. During these age periods the therapeutic problems pertaining to such defects are quite different from those encountered in older children It is therefore impossible to employ the same surgical or adults. measures which have proved to be so effective in repair of acquired (traumatic) diaphragmatic hernia of adults. Various authors have stressed the fact that congenital diaphragmatic hernia is a serious lesion which menaces the life of the individual. In 1931 Hedblom reviewed the literature and found that 75 percent of patients with the congenital form died before the end of the first month. In a review of the literature up to 1940 we are able to find but 31 cases treated by operation in the first year of life, and in only 17 of these did the patients survive. To this list of operative cases may be added our own series. While the total number of survivors is small, certain principles are now formulated which should insure recovery of 85 to 90 percent of these individuals."

Congenital diaphragmatic hernia does not always cause symptoms and may not be diagnosed except incidentally or at postmortem examination. When symptoms are present immediate operation is indicated. The severity of the symptoms is related to the number of abdominal viscera displaced into the thorax (246).

Symptoms and clinical findings in newborn infants are:

- 1. Cyanosis, which may be transient or persistent and which can be relieved temporarily by changing the infant's position.
- 2. Vomiting, which may be occasional or may occur after most of the feedings.
- 3. Dyspnea.

On inspection one side of the chest is found to move less well than the other. The percussion note may be dull or tympanitic on the affected side. The heart is displaced away from the affected side. On auscultation the breath sounds are distant or absent on the affected side and intestinal gurgles may be heard, which are diagnostic.

Roentgenographic studies quickly confirm the diagnosis. A flat film of the thorax, anteroposterior and lateral views, and in some cases views after a barium meal show the diagnostic points. Ladd and Gross (191, p. 337) emphasize the dangers of barium in increasing the chance of vomiting and of aspiration pneumonia, which should limit its use. "Film or fluoroscopic examination without the use of contrast media will usually give all the information that is required. . . The only cases in which barium studies are advisable are those with a hernia at the esophageal hiatus. In such patients it is important to know the length of the esophagus and size of the diaphragmatic opening when one is considering the desirability of surgical treatment.

"There can be no question that surgery is the treatment of choice in all these patients, except the occasional ones with a small esophageal hernia. There is sufficient evidence, from our own failures and from -the literature, to show the futility of expectant or medical measures. The general condition of the patient may be temporarily improved thereby, but no enduring improvement can be expected and the risks are great. The policy of waiting until the child is older and stronger is responsible for the loss of a great many lives which might be saved by an early operation. We are convinced that operation should be undertaken as soon as the diagnosis is made.

"On a theoretical basis, an operation performed in the first 48 hours of life is very advantageous, and we have had the opportunity of proving this in two cases. It is our experience that infants in the first 48 hours of life stand major surgical procedures extremely well—in fact, far better than they do at the end of a week or 10 days. Within the first 2 days the operator has the added advantage of dealing with an intestine which is not yet distended. This can easily make the difference between the possibility or impossibility of replacing intestines into the abdominal cavity."

Ladd and Gross (p. 347) describe in detail the very special operative techniques that they use. They report the cases of six infants operated on when 6 weeks of age or under, five of whom were cured and one of whom was symptomatically cured but had a slight recurrence of the hernia. They point out (p. 348): "It should be again strongly emphasized that in the last 10 years a change from a 75-percent mortality in infants with congenital hernias, as estimated by Hedblom (141), to an 85-percent recovery has taken place. The main factors bringing about this change are: resorting to operation in the first few days of life, the two-stage closure of the abdominal wall, improved surgical technic, and better preoperative and postoperative care."

Other defects

DISLOCATION OF THE HIP

Persistence of the fetal structures in the hip joint results in dislocation. This usually does not take place, however, until the child begins to kneel or stand. Chapple (62, p. 1206) says that this fetal condition of the hip joint, which is the forerunner of dislocation, may be recognized in infants, frequently as early as 2 months of age. He considers early recognition "extremely important, as treatment to be most effective must be started before the cartilaginous structures become malformed through the pressures applied on them by muscle pull and weight bearing." He points out the following signs:

- 1. External rotation of the thigh and angulation of the inguinal crease.
- 2. Beginning of shortening of the leg, shown by lifted gluteal and knee folds and the presence of an extra midthigh crease.
- 3. Limitation of abduction.
- 4. Absence of angulation in outer acetabular margin shown by roentgenograms.

Treatment, once the diagnosis is made, is an orthopedic problem.

CLUBFOOT

Clubfoot is frequently associated with spina bifida but may occur as an isolated defect. It is usually bilateral. The foot is held supine with the great toe pointing inward and downward (equinovarus). Since newborn infants' feet in the first days or weeks after birth are frequently held normally in a position that suggests clubfoot and since the muscles and tendons in this area are often relaxed, the diagnosis of clubfoot is often made incorrectly. Orthopedic advice should be sought when true clubfoot is present, as correction of position with bandages and in severe cases with plaster casts applied during the early weeks of life may be effective in overcoming the deformity. If these measures are not effective, surgical correction later may be necessary.

CLEFT LIP (HARELIP) AND CLEFT PALATE

Cleft lip and cleft palate are due to failure of the maxillary process to close as it normally does early in intrauterine life. According to Blair and Brown (38, p. 3) they "may occur in any degree from a slight notching of the lip or a slight split of the uvula to a complete cleft through the lip, alveolus, and hard and soft palates." If the lip only is involved, a cosmetic operation should be performed, according to Holt and McIntosh (155, p. 342), as soon as the infant's condition will permit—if he is vigorous, in the first 2 weeks of life. Blair and Brown state that it may be done in the first 24 hours. Since the infant's condition is the basis for the decision, Holt and McIntosh believe that it may be wise to postpone the operation if the infant is feeble or premature. When both lip and palate are cleft the lip defect should be repaired first.

When the palate is cleft the situation is serious, particularly in premature infants, as feeding is greatly complicated. Gavage or medicine-dropper feeding is required, in spite of which aspiration of milk is liable to occur, as well as secondary infection of the middle ear. Operation to close the defect must be done eventually but should be undertaken only by a skilled and experienced surgeon when the infant is of suitable age, is free from infection, and is in good nutritional condition.

MONGOLISM

The incidence of prematurity among mongols is relatively high, according to Gesell and Amatruda (111, p. 150). Recognition of the condition and its differentiation from cretinism are important. Gesell and Amatruda point out that though individual characteristics are not peculiar to mongolism, they present a distinctive composite, and the diagnosis can be made at birth, even in a premature infant. "The premature infant sometimes bears a mild, though wholly fictitious resemblance to the mongol, and errors of diagnosis are made if too much weight is placed on the obliquity of the eyeslits."

Since at the present time neither the cause nor the treatment of mongolism is known it will not be discussed here. The following list shows the characteristic diagnostic signs of mongolism and of cretinism, from which it must be differentiated.

	Mongolism	Cretinism			
Cause Head size	Not known Circumference smaller than chest at all ages. Outer canthus higher than inner Protrudes, normal size. Normal Normal Normal Subnormal Cardiac malformations Little finger frequently short. Normal Normal Vormal Little finger frequently short Normal Usually at birth	Thyroid deficiency. Normal. Protrudes, enlarged. Retarded. Normal. Thickened and dry. Retarded. Subnormal. Marked improvement. Low. Usually not under 6 months.			

Prevention of congenital malformations

Not only are methods of correction now known for types of congenital malformations hitherto considered invariably fatal but knowledge of their causes has so increased that it is possible to attempt prevention.

The very high incidence of congenital malformations in infants of mothers who have rubella in the early months of pregnancy has been shown. Pregnant women should be protected against exposure to rubella and possibly other virus diseases. If exposure to rubella is known to have occurred, pooled convalescent adult serum should be given according to Adams (4). It has been advocated (98, 92) that every female child be exposed to rubella before adolescence, though the existence of practical difficulties is recognized. Some physicians, including Murphy (241), believe that a therapeutic abortion is justified if rubella is contracted in the first 2 months of pregnancy, but Fox and Bortin (105) state that their records "do not justify consideration of termination of pregnancy because of rubella."

There is some evidence, thus far only suggestive, that a mother who receives an adequate diet during pregnancy may be less likely to have a congenitally malformed infant. In one study (55, p. 579) 7 of the 12 infants who had marked congenital defects were born to mothers whose diets during pregnancy were classified as poor to very poor, and 4 of the 12 to mothers whose diets were classified as fair or fair to poor. In animals congenital malformations have been produced experimentally as a result of vitamin-A and of riboflavin deficiency but the investigators call attention to the fact that in human beings this relationship has not been determined.

Some congenital malformations are known to be genetic in origin. In selected cases in which there is probability of inheritance of a serious type of defect, particularly one of the central nervous system, the physician should carefully weigh the question whether pregnancy is advisable, particularly if the woman has already borne one or more seriously defective infants.

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Some physicians consider that threatened abortion may be a sign of defective germ plasm. The physician's decision as to whether he should try to prevent abortion in these cases is one that must be made only after careful consideration of the medical and social aspects of each case. There is some evidence that pregnant women should not be given roentgen-ray or radium treatment.

Summary

Premature infants may be born with any type of congenital mal-. formation, and many of them die of defects that are amenable to surgical correction if promptly diagnosed. Major defects are those that are incompatible with life or require repair by major operations; minor defects impair function slightly or not at all.

Congenital defects are the result of heredity or of external factors such as roentgen-ray or radium treatment of the mother and maternal infection with rubella or possibly other virus diseases during early pregnancy or with toxoplasmosis. Maternal diabetes also increases the incidence of congenital defects. Deficient maternal diets have produced congenital defects in animal experimentation, and there is some evidence to suggest that in human beings a relationship may exist between inadequate maternal diet and defective offspring.

Premature infants are believed to be more prone to congenital defects than are full-term infants, though this is not the finding in all studies. The incidence of the various types of malformations in premature infants is not known. Among groups including both premature and full-term infants defects of the central nervous system are the commonest.

Diagnosis of a congenitally defective fetus in utero can sometimes be made by means of roentgenograms or suggested by a tendency to vaginal hemorrhage early in pregnancy or hydramnios later. During labor and delivery certain congenital defects such as hydrocephalus and large cystic kidneys may cause dystocia.

At birth, although some congenital defects are apparent, others are frequently overlooked because they involve internal organs or because they do not cause symptoms until later.

Early diagnosis of major defects is very important because many are now amenable to surgical correction. In some types of defects prognosis is directly related to prompt diagnosis and treatment; and in all types it is related to the skill of the operator and the adequacy of the supportive treatment and general care that the infant receives.

Among the commoner major defects that offer hope of surgical correction are hydrocephalus with meningocele; various defects of the gastrointestinal, biliary, and urinary tracts; certain cardiovascular abnormalities; diaphragmatic hernia; umbilical eventration; and some eye defects. Methods of diagnosing these conditions, as well as less common defects and defects for which the treatment has long been known and found successful, are discussed in considerable detail in the text. For discussion of methods of surgical treatment textbooks on the subject must be consulted.

The chances of prevention of congenital malformations have been improved by increased knowledge of causes.

Pregnant women should be protected from exposure to virus diseases, particularly rubella. Special precautions should be taken in the first trimester of pregnancy, as after this period danger of fetal injury by the virus is much less. Administration of immune serum should be tried if exposure has taken place. Immunization of all females prior to puberty by exposure to rubella has been advocated.

Every care should be taken that the pregnant woman receives an adequate diet since there is suggestive evidence that defects in the mother's diet may possibly play a role in causing congenital defects in the offspring.

A family history of the occurrence, in more than one generation, of a serious defect or the birth in a family of one or more infants with a serious defect, should be carefully considered by the physician as a possible contraindication to future pregnancies. Each case must receive individual consideration.

BIRTH INJURY

The term traumatic birth injury is used here to include contusions, lacerations, fractures, and hemorrhage caused by mechanical factors.

Potter and Adair (273, p. 111) have pointed out that "In a broad sense the term 'birth trauma,' like the term 'asphyxia,' may be used to include any condition which affects the fetus adversely during labor or delivery. Thus interference, from any cause, with transport of oxygen through the umbilical cord will result in injury to fetal tissues and, if sufficiently severe or prolonged, will result in permanent tissue damage or death. It is actually, therefore, injury sustained during birth. It seems advisable, however, to distinguish between the fetal damage caused by primary inadequacy of oxygen in the circulation and hemorrhage . . . caused by mechanical factors." The primary anoxemia (anoxia or asphyxia) is not included as a birth injury in this discussion. (For anoxia see p. 49.)

Premature infants are known to be peculiarly susceptible to traumatic birth injury because the various structures of the body—bones, skin, subcutaneous tissues, and blood vessels—are immature and therefore weak. Forces of labor and delivery that might be resisted by the structures of the mature infant may cause serious damage to the premature infant, particularly to the central nervous system.

Incidence

Data in regard to the incidence of birth injuries in premature infants are meager. For infants, presumably including premature infants, DePorte and Parkhurst (81) have given the most comprehensive report, based on data from birth and death certificates. They found that among 300,795 children born in New York State (exclusive of New York City) in 1940-42, 2,246 (0.7 percent) had birth injuries. Because of various inadequacies of reporting births and deaths due to birth injuries the authors made an estimate that the true incidence "would be four times the reported figures" (2.8 percent).

The authors point out that the reports on birth certificates do not represent the total incidence of birth injuries. Obviously all these cases cannot be diagnosed at birth. They found on examination of death certificates of infants dying under 1 month in the same 3-year period that 1,718 infant deaths were ascribed to birth injury. On 63.4 percent of the corresponding birth certificates the question in regard to injury was answered in the negative. In addition, they concluded that there were children on the "Crippled Children's Register" of New York State who suffered from orthopedic conditions resulting from birth injury who had not been reported on birth certificates as such.

The various types of birth injury reported by DePorte and Parkhurst were:

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Children with birth	injuries	¹ 2,	24	6
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Cerebral hemorrhage	3
Other head injuries (except forceps marks)	2
Fractures	1
Injury to the brachial plexus	1
Facial paralysis	2
Hematoma	1
Forceps marks, abrasions, contusions	7
Asphyxia	
Others and unspecified	1

¹ Forty-one children also had a congenital malformation.

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No data were given in this report on the maturity of the infants with birth injuries.

Potter reports two series of postmortem examinations of premature infants as follows:

From July 1, 1931, to July 1, 1941, postmortem examinations were made of 218 of 271 premature infants born alive (weighing 1,000-2,500 gm.). Of these 218 infants, 20 percent (44 infants) had "gross hemorrhage in the head or less commonly from the liver." In the next 5-year period (July 1, 1941, to July 1, 1946) 122 premature infants died. Postmortem examinations were made of 112 of them and 9 percent (10 infants) showed gross hemorrhage. (Personal communication from E. L. Potter, M. D., Chicago Lying-In Hospital. For other data with regard to these autopsies see **274**.)

Causes and prevention

Traumatic birth injuries are related to a variety of factors associated with labor and delivery. Injuries may occur alone or in combination (skin, subcutaneous tissues, bones, central nervous system and viscera). The prevention of these injuries is an obstetric problem and outside the scope of this book. It should be pointed out, however, that prevention of premature birth or prolongation of pregnancy to as near term as is compatible with maternal welfare will tend to prevent injury to the infant. Premature birth predisposes to birth injury because of (1) immaturity of the various body structures which makes them more liable to injury from slight trauma; (2) the relative frequency of breech presentation which is more frequently associated with injury than cephalic delivery; and (3) the frequency of rapid labor and quick expulsion from the birth canal.

In the discussion of the various types of birth injury their causes will be discussed and in most instances the means of their prevention will be obvious. In regard to central nervous system injuries the literature regarding causes and prevention is briefly reviewed.

Types of injury

Traumatic birth injuries may be slight or they may be of such a nature that they interfere with normal function or have an unfavorable prognosis for life or normal development.

INJURY TO SKIN AND SUBCUTANEOUS TISSUES

Injuries to the skin and subcutaneous tissues are relatively rare in premature infants. Abrasions, lacerations, contusions, edema, and

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hemorrhage due to localized pressure are likely to occur in prolonged and difficult labors, which are relatively infrequent in premature infants.

Caput succedaneum (edema of the scalp tissues) is due to arrested circulation in the expressed area of the head during labor after rupture of the membranes. Cephalhematoma is a severe type of sharply localized hemorrhage resulting from rupture of subperiosteal vessels. There may be superimposed edema of the subcutaneous tissue. Both these traumatic lesions, rare in premature infants, usually heal spontaneously. In cephalhematoma the blood may be absorbed rapidly or slowly. Slow absorption may result in the formation of a calcified nodule, which may persist for some time but is usually absorbed eventually.

In frank breech deliveries the skin may be bruised by the pressure of the operator's fingers. Sudden or prolonged changes in pressure may cause edema or extravasation of blood into the tissues around the rectum and in the labia or scrotum. Less marked pressure changes may cause merely edema, a common site of which is the scrotum. Extensive hemorrhage may cause serious injury of the testicles and scrotum during breech delivery. Traumatic hemorrhages must be differentiated from those of so-called hemorrhagic disease; scrotal edema, from true hydrocele.

Sternomastoid muscle injury is due to forcible turning of the head or pressure of a forceps blade during delivery. A localized hemorrhage may occur which may calcify and then absorb. In rare instances, permanent torticollis results.

In all of these cases treatment consists in protection from further trauma, prevention of secondary infection and local treatment appropriate to the type of lesion.

INJURY TO BONES

The various types of injury to bones occur relatively infrequently in premature infants.

The clavicle is the commonest site for fracture, which may occur in vertex or in breech deliveries. The diagnosis may not be made until a hard mass is noticed which proves to be due to callus formation. Sanford (303) found a unilateral Moro reflex useful as a diagnostic sign. The Moro reflex is elicited by startling the infant (clapping the hands or banging with the fist on the examination table). The normal infant reacts by drawing up the legs and extending the arms in an "embrace" position. The response is symmetrical in all four extremities. McEnery (224) has pointed out that the unilateral reflex is found in other conditions such as brachial palsy, cerebral injury, and fracture of the humerus. He finds that if, on simultaneous palpation of the contours of both clavicles, the supraclavicular space is obliterated by muscle spasm on the affected side this is the most reliable diagnostic sign of fractured clavicle.

Spontaneous healing without deformity is usual; union occurs in about 10 days and absorption of the callus takes place gradually. The infant should be handled carefully in order to avoid further trauma to the clavicle. For example, the arm on the affected side should not be introduced into the shirt sleeve. The shirt itself will tend to splint the arm. According to Stone (337) it is only in cases of marked displacement of the fragments that more thorough immobilization is required.

The long bones of the arm or leg may be traumatized during delivery in a variety of ways. Stone (337, p. 185) finds that injuries to the humerus consist chiefly of luxation at the shoulder, epiphyseal detachment and fracture of the diaphysis. The elbow and forearm are rarely injured. These injuries are sustained more frequently in breech than in vertex deliveries. Injury to nerves is an occasional complication.

Injury to the femur takes place usually in footling deliveries involving traction on the feet. The periosteum near the epiphysis may be torn with resulting hemorrhage. Calcification of extravasated blood may be demonstrable in roentgenograms. Healing is spontaneous. In this type of delivery the femur may be fractured, usually in the upper third.

The chief diagnostic sign of fracture of the arm or leg is the absence of spontaneous movement of the affected extremity. The site of fracture may be palpable and crepitus may be present. The diagnosis may be confirmed by roentgenograms except when the injury involves an epiphysis that has not yet calcified.

Treatment of these injuries to the bones of the extremities is an orthopedic problem.

INJURY TO PERIPHERAL NERVES

The commonest site of peripheral nerve injury is the facial nerve. In forceps delivery the facial nerve is commonly injured near its exit from the stylomastoid foramen. The prognosis in facial paralysis is good and no treatment is needed. The radial nerves may occasionally be injured by pressure from forceps or in fractures. \bullet

There are no data available to show the incidence of brachial palsy in premature infants. This type of paralysis has been found to be most often associated with breech deliveries, and since breech delivery is much more frequent among premature than among mature infants, it is possible that this type of injury might be found more often among premature infants.

The roots of the brachial nerves may be injured by direct pressure, by tearing, by stretching, or by avulsion from the cord. Injury to the brachial plexus results in paresis or paralysis.

There are three types of brachial palsy:

- 1. Upper-arm paralysis (Erbs type). This is the commonest type and is due to stretching or tearing of the fifth and sixth cervical roots. It may involve the phrenic nerve also.
- 2. Lower-arm paralysis (Klumpke type). This is a relatively rare type and is due to stretching or tearing of the first thoracic and eighth cervical roots. The cervical sympathetic nerve may be involved also.
- **3.** Whole-arm paralysis.

According to Ford (104, p. 902) the following are the possible mechanisms involved in brachial nerve injuries:

- 1. In breech delivery from :
 - a. Traction on the shoulder in delivery of the head.
 - b. Forcible elevation and abduction of the arm when traction is made on the arm in delivering the trunk.
 - c. Traction on the trunk.

- 2. In vertex delivery from:
 - a. Drawing of the head and neck away from the shoulders in an effort to deliver the shoulders.
 - b. Pressure of the finger in the axilla.

When traction is made on the trunk in breech delivery the spinal cord is usually injured also so that the primary lesion may be in the cord rather than in the roots or trunks of the plexus. In both types of delivery associated bone injuries—fracture of the neck or shaft of the humerus or separation of the epiphysis or fracture of the clavicle may result in brachial nerve injury.

Clinical signs

- 1. Erbs type: Flaccid paralysis of the upper arm seen shortly after birth; usually unilateral; typical posture of arm, adduction and internal rotation; extension at the elbow and often pronation of the forearm and some degree of flexion at wrist. The Moro reflex is absent on the affected side. The phrenic nerve may be involved and then paralysis of the diaphragm occurs.
- 2. Klumpke type: Usually unilateral; distal paralysis of arm; sensation may be impaired; weakness of hand and wrist; if sympathetic fibers of first thoracic root are injured small pupil and lid droop on same side.
- 3. Paralysis of whole arm: Reflexes are lost, muscles waste, and there is anesthesia.

Diagnosis

Differentiat diagnosis must be made from :

- 1. Cerebral palsy—which, although flaccidity may be present early, results in spastic paralysis. In cerebral palsy the legs are usually involved also.
- 2. Hand paralysis due to lesion in nerve trunk. If the cervical sympathetic nerve is involved this favors the diagnosis of brachial-plexus injury.
- 3. Pseudoparalysis due to:
 - a. Bone and joint injury—muscles are held rigid to immobilize parts because of pain.
 - b. Syphilitic involvement of bones—lesions usually obvious in roentgenograms.
- 4. Injury to the cord. Paresis or paralysis of the legs and anesthesia corresponding to the nerve injury are evidence of cord injury; if the legs are not involved it is difficult to differentiate cord injury from the Klumpke type of palsy. The peripheral nerves and the cervical sympathetic nerve may be involved as well as the cord.

Treatment

Treatment of brachial palsy has been outlined by Ford as follows:

- 1. Place arm in splint within the first few days.
- 2. After 2 to 3 weeks remove splint for a short time daily.

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- 3. Give gentle massage and passive movements.
- 4. When power begins to return give exercises,

5. Operation to suture nerves. Ford advises that this should be reserved for cases in which "no signs of recovery are observed after a year of proper orthopedic treatment."

INJURY TO THE CENTRAL NERVOUS SYSTEM

Birth trauma may cause injury to the brain from (1) contusion without hemorrhage, or (2) hemorrhage into the meninges, the brain substance, or the ventricles.

Compression of the brain (contusio cerebri)

Contusio cerebri is the name given to this symptom described by Seitz. Grulee and Bonar (132, p. 224) say: "In the mildest form it probably manifests itself in the marked apathy, somnolence, and anorexia not uncommonly seen in the first few days of life. In the more serious forms the infant is irritable and twitchings or convulsions may be present. The condition at all times is practically impossible to differentiate from the cerebral symptoms of intracranial hemorrhage. Early recovery speaks for contusion. In the occasional cases coming to autopsy there is hyperemia and edema of the brain, and according to Schwartz, foci of softening in the brain sub-stance." Ehrenfest (96) discusses this condition, which he considers to be the result of intracranial hypertension. He states (p. 39): "Seitz acknowledged that such fleeting signs of an intracranial lesion might, however, also be produced by a slight and transient edema, or, as is claimed by other authors, even by small hemorrhages." He quotes Cruickshank to the effect that edema and intracranial tension are factors of first importance in a large proportion of neonatal deaths. Rydberg (302) made a clinical and pathologic study of cerebral injury in newborn infants. Among 34 infants with "major cerebral symptoms" that died, there were 6 (of whom 2 were premature) in whom "no intracranial bleedings of any importance were found" but "a considerable degenerative tissue change in the brain was observed." He considers that the most acceptable explanation of the changes is interference with circulation in the brain due to compression of the head during delivery.

Concussion (contusio cerebri) is difficult to distinguish clinically from intracranial hemorrhage and sometimes is indistinguishable except postmortem. As a rule, however, these infants when they survive show relatively rapid improvement and complete recovery in contrast to the gradual progression of symptoms shown in cases of intracranial hemorrhage.

Anderson (23, p. 232) finds the Moro reflex helpful in differentiating between edema of the brain and hemorrhage. In the former this reflex is absent early but present after a few days when the edema has subsided; in the latter the reflex is present immediately after birth but is absent later if damage has been done to the brain.

Intracranial hemorrhage

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Premature infants are known to be particularly susceptible to intracranial hemorrhage during birth. There is wide variation in reported incidence even among full-term infants, depending largely on whether the diagnosis was based on clinical findings in living children or on postmortem findings. Ford (104, p. 876) found that the incidence of intracranial hemorrhage in stillborn infants and live-born infants who died within a few days after birth, as reported in six studies, varied from 20 to 44 percent; but he says, "in children born by breech delivery, and especially in premature children, the figures are even higher. . ."

Kunstadter (189, p. 240) reported the incidence of intracranial hemorrhage among 1,427 infants admitted to the Premature Infant Station of Sarah Morris Hospital, Chicago. Of the 440 infants that died, autopsies were performed on 342, and evidences of intracranial hemorrhage were found in 154 (45 percent). Among 987 infants that "were graduated," 102 (10.3 percent) "were considered . . . to have sustained intracranial hemorrhage." The total number of cases of intracranial hemorrhage was 256, an incidence of 17.9 percent of 1,427 infants.

Sites and causes of intracranial hemorrhage in premature infants

During birth a variety of traumatic injuries to the central nervous system may occur which may cause intracranial hemorrhages. In a small proportion of cases the hemorrhages are associated with fracture of the skull.

It has been shown in postmortem studies that in premature infants the most frequent sites of hemorrhage differ from those found in fullterm infants.

Hemsath (144, p. 348) reports a series of 414 autopsies (164 "fresh stillbirths" and 250 newborn infants) from two New York hospitals. He found, in 54 cases of subdural hemorrhage, that only one-third were in premature infants, whereas in 19 cases of intraventricular hemorrhage 16 were in premature infants. (See fig. 25.)

Studdiford and Salter (338, p. 217) also found at postmortem examination differences in the lesions of full-term live-born and stillborn infants and those of premature live-born and stillborn infants born before the thirty-fifth week of gestation. In 20 term infants the lesions were dural lacerations or subdural hemorrhages in every case, whereas in 38 premature infants of less than 35 weeks' gestation these lesions were relatively rare, the common ones being arachnoid or subventricular hemorrhages. In the 7 more mature premature infants (35 to 38 weeks' gestation) the findings were intermediate between the other two groups. In no case was the type of lesion characteristic of premature infants found among term infants.

Craig (69) made a clinical and postmortem study of 126 infants with intracranial hemorrhage, 67 of whom were premature. He found (p. 113) that the type of cerebral hemorrhage varied according to the maturity of the infants, as is shown in table 52.

It can be seen that subarachnoid and intraventricular hemorrhages were found much oftener in premature infants than in mature infants. Subdural hemorrhages and hemorrhages into the brain substance were, on the other hand, much more common among mature infants.

Subarachnoid hemorrhages are described by Craig (p. 96) as follows: "Bleeding resulted from capillary oozing and not from any localized intracranial injury. The hemorrhage varied in extent and distribution. In some cases it was most marked over the vertex; more commonly it was related to the occipital and posterior parietal surfaces; usually bilateral, it was limited to one cerebral hemisphere in a few cases.



Figure 25.—Intraventricular hemorrhage in a premature infant weighing 780 gm. (courtesy Edith L. Potter, M. D., Chicago Lying-In Hospital).



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		Percent			
Type of intracranial hemorrhage	Total	Mature and postmature infants	Premature infants 1	Premature infants ³	
Total	126	59	67	53. 2	
Subdural	62	43	19	30.6	
With tentorial tears Without tentorial tears Subarachnoid Intraventricular Intro brain substance	42 20 36 22 6	33 10 7 3 6	9 10 29 19	21. 4 50. 0 80. 6 86. 4	

TABLE 52 Maturity in relation to type of hemorrhage (Craig)

¹ Four of these infants had evidences of hemorrhagic diathesis. ³ Calculated from Craig's figures.

"The picture of severe leptomeningeal hemorrhage was characteristic. Cerebrospinal fluid was present in excess, and the brain was completely enclosed within a reddish-yellow layer of jelly-like consistence. . . . The meninges were sodden and congested and floated on a heavily blood-stained fluid separating them from the brain substance."

Intraventricular hemorrhage, according to Craig (p. 101), "was associated with capillary oozing of limited extent into the subarachnoid space in four, and with isolated minute cortical hemorrhages in three cases. Massive intraventricular bleeding resulted in increase in the size of the brain and marked flattening of the convolutions over the vertex. The source of the hemorrhage was the veins of the choroid plexus in fourteen, and the superficial veins in the ventricular wall in two cases . . . Bleeding occurred from both these sites in four instances, and in two its origin was not found. Hemorrhage followed acute engorgement of the veins or occurred as a sequel to thrombosis. . . . [without evidence of infection].

"Hemorrhage was invariably gross. Blood was found throughout the entire ventricular system in several cases. . . . It was usually present only in the lateral ventricles and occasionally was confined to the posterior horns, or was limited to one side. . . . Gross destruc-tion of brain tissue was present in seven cases . . ."

In the two groups of cases (those with subarachnoid and those with intraventricular hemorrhage) Craig states that atelectasis was a common finding as well as pneumonia and hemorrhage into the lungs. Bleeding also occurred into serous cavities, intestinal wall, and suprarenal glands.

Ylppö (409, p. 484) has found: "At necropsy the smallest premature infants show extensive intracranial and intraspinal hemorrhages with striking frequency; the lower the birth weight of the child, the more frequently is hemorrhage present. These intracranial hemorrhages are found chiefly under the dura, in the pia, or in the subarachnoid space, and very often also in the brain substance itself. . . . The favorite location of these hemorrhages is on either side of the midline and chiefly in the posterior portion of the two hemispheres; often just in the region of the motor area for the legs. The spasticities of Little's disease can be easily produced by these brain hemorrhages. Often in these small prematures the whole brain floats in a serosanguineous fluid, and the pia and arachnoid frequently envelope the whole interior surface of the cerebellum like a bloody hood; and here at times a large hemorrhage . . . likewise occurs. These hemorrhages around the cerebellum and the medulla oblongata have a special significance in relation to the frequent attacks of asphyxia in prematures. . . . Hemorrhages into the vertebral canal are usually extradural. . . ."

The significance of multiple petechial hemorrhages in the brain and meninges has long been a subject of discussion. They may be found associated with trauma, congenital syphilis, hemorrhagic disease, and simple asphyxia without trauma, in all of which conditions the petechiae are usually found in the viscera also. Multiple petechial hemorrhages in the brain may be simply a symptom of asphyxia or a cause of asphyxia. Cruickshank (73) states that in autopsies on 800 infants dying in the neonatal period, oozing from the meninges was found to be almost universal in the infants that died from the effects of asphyxia. He describes it as a not uncommon finding in premature infants.

Munro and Eustis (239, p. 279) say: "... asphyxia should be given at least a temporary recognition as an etiologic factor in the production of intracranial hemorrage in the newborn and [we] propose, therefore, to modify Warwick's classification in such a way as to include such cases in a separate division. Since we have done this, we have found that the number of cases of intracranial hemorrhage which might properly be classed as traumatic in origin is relatively quite small. Nevertheless, as long as fracture of the skull occurs, and as long as there continues to be a tearing of the sinuses and meninges by excessive overlapping of the sutures, so long will it be necessary to classify certain of these cases as strictly traumatic in origin. Our classification is as follows:

- "1. Traumatic group—hemorrhage caused by excessive molding of the head and overriding of the sutures.
- "2. 'Asphyxia' group—hemorrhage caused by excessive cerebral venous congestion with rise of intracranial pressure.
- **"3.** Fetal disease group—the hemorrhage in these cases having no relation to the labor, but being most commonly caused by hemorrhagic disease and rarely by syphilis or other toxemias."

As a differential point Potter and Adair (273, p. 148) state: "Asphyxial hemorrhage is always smaller in amount than that produced by trauma. It is probable that severe cerebral congestion and extravasation of erythrocytes into the subarachnoid space are due to capillary injury produced by anoxemia rather than to local trauma. This is also true of hemorrhage into the lateral ventricles. Microscopic hemorrhages in the brain substance are found most frequently in the pons, in the medulla, and in the region of the lateral ventricles, and are similar in origin to petechiae produced by anoxemia in other parts of the body."

Subdural and intraventricular hemorrhage result, according to Ehrenfest (96, p. 46), from molding of the head with overlapping of adjoining cranial bones. The dura, folded and stretched, may break if it is abnormally fragile and if the overlapping is excessive or sudden, resulting in dural hemorrhage; or the veins at either side of the longitudinal sinus may be torn or the sinus itself may rupture. Sudden or severe lateral compression of the head resulting in elongation of the antero-posterior diameter may cause tearing of the upper tentorial sheath where it joins the fibers of the falx or tearing of the vena cerebri magna, thus causing intraventricular hemorrhage. Forceps extraction of the head through the incision made at cesarean section or sudden or excessive compression of the head when extracted through too small an incision may cause tentorial tears. When the membranes rupture prematurely the head, if it is the presenting part, is subjected to strong and direct pressure and in breech delivery there is increased pressure on the aftercoming head before delivery is complete, either of which may cause tentorial tears. A contributory factor in causing hemorrhage noted by Ehrenfest is congestion due to the squeezing of blood into the upper part of the body as the lower part passes through the cervix and the vulvar ring.

In premature infants the chief factors that play a role in producing the lesions characteristic of intracranial hemorrhage are associated with precipitate delivery after short labor, premature rupture of the membranes, and breech delivery, all of which are much commoner in premature than term deliveries. Associated factors are the fragility of the structures, including the blood vessels, and the tendency to bleeding because of prolonged prothrombin time.

Diagnosis

The diagnosis of intracranial hemorrhage in premature infants in the early neonatal period is especially difficult because the symptoms and signs are usually generalized, and the condition must be differentiated from a variety of other conditions causing similar symptoms.

Grulee and Bonar (132, p. 234) point out that, in newborn infants, it is difficult to characterize the symptoms of certain types of hemorrhage. There may be:

1. Massive hemorrhage.

- a. With practically no symptoms, the child dying almost immediately after delivery,
- b. With labored breathing, cyanosis, twitching or convulsions, and bulging fontanel appearing at or shortly after delivery.
- In these cases one finds at postmortem examination a very large hemorrhage of the vertex, or the base, or both, and evidence of a great deal of pressure.
- 2. Slight hemorrhages caused by rupture of small vessels within cranial cavity.
 - With gradually developing symptoms, usually after 24 to 48 hours, such as lethargy, refusal of food, gradually increasing pallor, slight twitching, later local or general convulsions, increased tension of fontanel, and cyanosis.

These authors point out two important points in relation to the diagnosis of intracranial hemorrhage in newborn infants:

1. That the focal symptoms cannot be relied on to localize the brain lesion.

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2. That other factors than trauma may be responsible in whole or in part for the hemorrhage. Hemorrhagic disease or asphyxia may play a role in slight hemorrhages.

The essential early symptoms and signs indicative of intracranial hemorrhage in the order of their frequency given by Kunstadter (189, p. 248) are shown in table 53.

Symptoms	Number	Percent	
Cyanosis	· 64	92. 75	
At Dirth (80). Delayed (14). Inability to nurse.	20	29.0	
Jaundice (severe)	19 15	27.5 21.5	
"Brick-red color"	13 11	18.8 15.9	
Convulsions	8	13.0 11.6 11.6	
Muscular twitchings	7	10. 1	

TABLE 53 Symptoms of intracranial hemorrhage (Kunstadter)

Differential diagnosis is difficult, particularly among premature infants. In cases of sudden death in the first hours after birth it is usually safe to assume that extensive intracranial hemorrhage has occurred. In cases of smaller hemorrhages and gradually developing symptoms the condition must be differentiated from contusion (see p. 227), asphyxia, sepsis, eyrythroblastosis (Rh incompatibility), and hemorrhagic disease.

Examination of the spinal fluid may be useful in making the diagno-The interpretation of findings is, however, often difficult. The sis. trauma of the puncture alone may produce bleeding from injury of a vessel in the spinal canal; a yellowish fluid may be obtained which may be evidence of icterus neonatorum and not of hemorrhage. If the test for albumin (Nonne) in the yellow spinal fluid is strongly positive, this is evidence of hemorrhage. Such xanthochromic fluid is the result of decomposition of blood and would be found only several days after the hemorrhage had stopped. If crenated or broken-down red blood cells are present in fresh spinal fluid, these are evidence of true intracranial hemorrhage if no previous lumbar puncture has been made. In the 69 cases described by Kunstadter (p. 250), lumbar puncture was performed on 14 infants. In every instance the findings were positive. In 7 cases the fluid was bloody and in 7 others it was xantho-Red-blood cells were frequently found on microscopic exchromic. amination of xanthochromic fluid. There may be some danger in the procedure since the way in which the infant must be held (with the spine and neck flexed) results usually in crying, which tends to increase intracranial pressure. In some cases it may be necessary, for diagnostic purposes, to tap the cisterna magna or the ventricle.

In the later stages, when definite evidences of damage to the central nervous system have developed, such as spasticity, paralysis, and convulsions, great judgment is required to make a differential diagnosis between birth trauma and congenital cerebral defects. Ford (104, p. 895) states that the diagnosis of birth trauma "depends chiefly on the history of birth, but in the writer's opinion the character

Birth Injury

of the clinical picture is of distinct importance in the differential diagnosis." Ford considers that hemiplegia, monoplegia, and asymmetrical palsies are more likely to be due to birth injury than to congenital defects of development. The distinction between double hemiplegia and severe diplegia is often difficult or impossible.

Treatment

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In the acute stage of intracranial hemorrhage the treatment consists in certain general measures as well as certain specific procedures in some cases.

The following general treatment should be given:

- 1. Keep the infant warm and disturb him as little as possible.
- 2. Elevate the infant's head slightly.
- **3.** Give vitamin K intramuscularly at once and repeat if the prothrombin time continues to be prolonged. (See p. Ž95.)
- 4. Give oxygen if cyanosis is present. (See p. 120.)
- 5. Give fluid subcutaneously since during the period of acute symptoms the infant should not be fed. Small transfusions of citrated blood also are indicated.
- 6. Give sedatives if the infant is restless, hyperactive, or convulsive.

In regard to specific methods of treatment there is considerable

difference of opinion as to the value of repeated lumbar punctures. Ford (104, p. 888) states: "A number of writers claim that spinal drainage by repeated puncture is a valuable therapeutic measure. This they say is helpful in reducing the increased intracranial pressure and in removing blood from the meninges which may lead to a serious meningeal reaction. The writer is not convinced that all these claims are justified. It is clear that small or moderate amounts of blood are usually absorbed promptly from the subarachnoid spaces and leave no appreciable ill-effects. Hemorrhages into the brain or the subdural space, of course, cannot be affected in any way by spinal This statement is also true of encapsulated hematomas in puncture. the subarachnoid spaces. It is possible, moreover, that the struggling of the infant during spinal puncture and the relief of pressure due to release of fluid may play a part in prolonging the bleeding or even in starting it again after it has stopped. The possibility of precipitating herniation of the medulla into the foramen magnum and causing paralysis of respiration must be kept in mind. Despite all these objections, there is no doubt that spinal puncture, if performed properly and with adequate judgment, is of value in reducing intracranial pressure and removing hemoglobin from the meninges. Obvious symptomatic improvement often follows the removal of 15 or 20 cc. of blood-stained fluid."

In regard to surgical treatment, Ford states that in his experience operation in the early stage to remove fluid blood or clots is not indicated. Later, in the chronic stage, if symptoms persist and give evidence of a localized lesion, exploration may be justified provided the services of a surgeon skilled in brain surgery and in operating on small infants are available.

When the child develops palsies (hemiplegia or diplegia) or epilepsy, Ford states that although craniotomy to remove scars or cysts has been advised by some, in his opinion "good results are exceptional."

Later development

There has developed, as the result of one of the earliest reports on the fate of a group of premature infants, an impression that the outlook for these infants, as far as the nervous system is concerned, is generally bad. In later, more carefully conducted studies, the outlook for these infants has been shown to be less gloomy. It is, however, true that premature, as well as full-term, infants who suffer from intracranial birth trauma have a poorer prognosis for normal development than do uninjured infants. In individual infants the prognosis should be guarded until the infant has reached the development at which mental tests are reliable.

The most comprehensive follow-up study of premature infants that survived intracranial hemorrhage is that of Kunstadter (189, p. 259). The study was based on a group of 69 infants, 20 of whom weighed 1,000 to 1,500 gm. at birth, 31 between 1,500 and 2,000 gm., and 18 between 2,000 and 2,500 gm. Of the 69 infants, 42, who were repeatedly examined, showed "no physical evidence of injury to the central nervous system and their weight and growth curves compare favorably with the general group of 250 infants." Twenty-seven in-

TABLE 54	Infants show (Kunstadter)	ing evidence	of intracranial	injury	at last	examination
		1				

Present findings	Mental status	Birth weight (gm.)	Sex	Early symp- toms	Late symp- toms ¹	Present age
I. Severe injury:						
1. Spastic tetraplegia	High-grade mentally defec-	1,985	F	+		6 years.
2. Hydrocephalus	do	1,470	F	+		21/2 years.3
Spastic tetraplegia	Average	1,785	F	+		8 months.
4. Spastic diplegia	do	1,710	M	1 +		4 years.
5. Spastic diplegia	do	1,250	M		+	11 months.
Spastic tetraplegia	Dull and backward	2,010	F	+		17 months.
Spastic tetraplegia	Imbecile	1,480	M	1 +		11 months.
Spasticity, marked	Dull and backward	2,285	M	+		6 months. ³
9. Spastic paraplegia	do	1,780	F	+		8 years.
10. Spastic paraplegia	High-grade mentally defec- tive.	2, 235	м		+	15 months.
11. Spastic tetraplegia	Average	1,230	м	+		51/2 months.
II. Moderate injury:						
1. Hydrocephalus	Imbecile	2,385	м	+		18 months.
2. Spasticity, moderate.	High-grade mentally defec- tive.	1, 730	F	+		22 months.
3. Spasticity, moderate.	A verage	1.920	м	+		6 months.
4. Spastic monoparesis	Dull and backward	1.475	F	1 +		21/2 vears.
5. Strabismus, nystag- mus.	High-grade mentally defec-	1, 885	Ň		+	2 years.
6. Hypotonia	Average	1.685	м		+	21% vears.
7 Spasticity, moderate	do	1,410	M		+	Do.
III. Slight injury:		-,				20.
1. Exaggerated deep re-	do	1, 905	м	+		$5\frac{1}{2}$ months.
2 Strahismus		1 280	F	1		6 veers
3 Evaggerated deep re-	do	2,200	ŵ			Alé monthe
flavos		2,000	141			4/2 11011015.
4. Exaggerated deep re-	Dull and backward	1,680	м	+		$8\frac{1}{2}$ months.
5. Weakness right arm	Average	1,630	м	+	•••••	21 months.
6. Exaggerated deep re-	do	1, 965	м	+		4 years.
7. Exaggerated deep re-	Superior	2, 135	м		+	3 years.
nexes, strabisinus.	Fachlamindad	1 200	17			4
5. Spasticity-right leg	reepieininged	1,380	r	1 + 1		4 years.
9. Exaggerated deep re- flexes.	Average	2,300	м	+		o years.

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No symptoms until after graduation from station.
 Died of pneumonia at 3 years.
 Died of pneumonia at 1 year.

Birth Injury

fants (see table 54) showed evidence of damage to the central nervous system, which was classified as "severe" in 11 cases; "moderate" in 7; "slight" in 9. Thirteen of these 27 infants were found to be mentally retarded.

Spinal-cord injury

Birth injury to the spinal cord is usually the result of stretching due to traction in breech delivery or to fracture of a vertebra.

Incidence

To Crothers (71) belongs the credit for drawing attention to the comparative frequency with which injury to the cord takes place during breech delivery. Since breech delivery of premature infants is relatively common it would be expected that spinal injury would occur more frequently in these infants. Reports of this condition in premature infants are, however, relatively rare. This may be due in part to the ease with which premature infants are delivered and in part to the fact that, as Crothers has pointed out, the condition is usually not recognized unless routine examinations of the spine and cord are made postmortem. The great majority of cases reported by Crothers and Putnam (72) were full-term infants delivered with difficulty. In their series of 28 infants with spinal-cord injury 2 were stated to be prematurely born. The case histories of these 2 infants are given below in abstract form.

- Case 2. A premature infant delivered by difficult version and extraction at 8 months. The mother was a nephritic. When seen at 9 years of age the child had signs indicating almost complete transection of the cord in the lower thoracic region.
- Case 19. A premature infant delivered by version at the sixth month because the mother had an antepartum hemorrhage. The infant weighed about 2 pounds. The signs in the infant were those of diffuse injury of the thoracic cord due to stretching. There was weakness of the lower trunk due to anterior horn cell damage and moderate spasticity due to impaired pyramidal tracts.

Pierson (260) also stresses the serious consequences to the infant of breech delivery. He pointed out that birth injury and shock in breech deliveries cause greater fetal mortality and morbidity than asphyxia. In a series of autopsies on 36 infants delivered by the breech, spinal-cord hemorrhage was found in 17, and fractured vertebrae in 14. None of these 36 infants were reported to be premature.

Causes

Crothers (71) points out that the mechanisms that may cause cord injury in breech delivery are: traction exerted over the entire length of the vertebral column and of the cord, which may result in hemorrhage or rupture; and direct pressure on the head resulting from uterine contraction or due to direct suprapubic pressure by the operator or assistant, which also favors central nervous system damage.

Both the maneuvers cited are, according to Crothers, "extremely likely to favor herniation of the medulla" into the foramen magnum. The obstetrician, he points out, considers that asphyxia is the chief danger in these cases and to prevent it regards speed in extraction as essential.

Diagnosis

Diagnostic signs are (1) respiratory difficulty (from pressure on medulla or involvement of phrenic nuclei); (2) paralysis of abdominal muscles and legs; (3) loss of sensation as high as the costal margins or higher.

Crothers (p. 110) has pointed out that the diagnosis in fatal breech cases is usually "asphyxia," but fracture with transections and hemorrhage of the cord should be suspected in all such deaths. He states that injury to the cord in the cervical region is usually fatal because of the proximity of the lesion to the phrenic nerves and the medulla. Transections below "the fatal level" result in anesthesia and flaccid paralyses, the distribution of which depends on the site of the cord lesion.

Crothers and Putnam (72, p. 121) point out: "Often the diffuse nature of the lesions made accurate focal diagnosis difficult and relatively futile." In some cases the signs are difficult to differentiate from cerebral injury. The same child may have injuries of the cord, the brachial plexus, and the brain. In these cases, although the paralysis is a flaccid type, reflex activity of the isolated portion of the cord is not usually abolished. In incomplete injuries there may be spasticity, flaccidity, ataxia, total or partial anesthesia, and so on in almost any combination.

Treatment

Ford (104, p. 901) states that "during the early stages of spinal cord birth injury the child must be nursed very carefully and every effort made to prevent bed sores and urinary tract infection. Later various orthopedic measures may be useful just as in any other spinal injury."

Chance for complete recovery of function of paralyzed parts is nil.

VISCERAL INJURY

The liver and suprarenal glands may be injured during birth, or after birth in the course of attempts to resuscitate the infant. In Potter and Adair's experience these injuries rank next in frequency to intracranial hemorrhage as a fatal condition caused by trauma (273).

Injury to liver

Ehrenfest (96, p. 286) states that by far the commonest of the abdominal organs to be thus injured is the liver. Petechial hemorrhage may occur when the infant is asphyxiated; there may be subcapsular hemorrhages found particularly after difficult breech deliveries; there may be rupture of the capsule; or there may be deep ruptures into the liver substance leading "to serious or fatal intraperitoneal hemorrhage." The liver may be injured by compression during efforts to resuscitate the infant. Ehrenfest cites the case of a small premature infant reported by Hedrén which, he states, is unique because the delivery was spontaneous and rapid in breech presentation and there was no external injury and yet the liver was ruptured. In most cases of liver injuries reported the infants are large and delivery is difficult and by breech.

Ehrenfest states that infants "eventually dying from a ruptured liver, apparently, as a rule, seem perfectly normal for approximately the first 3 days of life. Symptoms of serious illness do not manifest themselves until a considerable amount of extravasated blood has





Figure 26.—Rupture of both adrenal glands with massive hemorrhages (breech delivery) (courtesy Lewis K. Sweet, M. D.; and John L. Parks, M. D., Washington, D. C.).

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reached the peritoneal cavity. Then death is prone to occur suddenly and unexpectedly." Postmortem examination reveals the true cause of death which otherwise might be ascribed to "asphyxia, debility or intracranial injury."

Other injuries

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The spleen and the kidneys, on the other hand, although the site of petechial hemorrhages in cases of severe asphyxia, are very rarely the site of severe traumatic hemorrhage.

The suprarenal glands may be damaged during birth, particularly by manipulations in which the baby is grasped around the waist and the trunk is twisted. The lesions found are parenchymatous hemorrhages or rupture. (See fig. 26.) Browne (48) found, in a pathologic study of 400 stillbirths and neonatal deaths, 27 instances of suprarenal hemorrhage, in only 6 of which the child was born alive. He pointed out that this accident is found almost entirely in cases of difficult forceps and of breech delivery; it was found to be 22 times as likely to be associated with breech delivery as with delivery by the vertex, and about 3 times as likely to occur in premature labors as in labors at term.

Summary

The term birth injury is used to include contusions, lacerations, fractures and hemorrhages caused by mechanical factors. Asphyxia resulting from conditions surrounding birth is not included in this classification.

Premature infants are peculiarly susceptible to birth injury because of immaturity of the various body structures and tissues. Data are not available on the incidence of birth injuries in premature infants; in newborn infants (full-term and premature) an estimate of 2.8 percent of births has been made. In a postmortem study of 503 neonatal deaths 13 percent were found due to traumatic birth injury, and all of these infants were premature.

Among the minor birth injuries are those of the skin, subcutaneous tissues, and some bone and peripheral nerve injuries. These injuries are relatively infrequent in premature infants.

In all of these cases treatment consists in protection from further trauma, prevention of secondary infection, and local treatment appropriate to the type of lesion.

Major birth injuries include severe peripheral nerve and bone injuries, injuries to the brain and cord, and rupture of viscera. All of these injuries are relatively frequent in premature infants because of the delicacy of the structures and the frequency of breech presentation.

Brachial palsies are most often associated with breech deliveries but may also occur in vertex deliveries. The most serious injury is brought about by traction on the trunk, for it is in this way that the spinal cord is injured.

Differentiation of types of brachial palsy in premature infants is a neurological problem that differs in no way from the problem in mature infants. It is important to determine the extent of injury and to differentiate the condition from other types of arm paralysis such as those due to cerebral and spinal injury, pseudoparalysis resulting from bone or joint injury, and syphilitic periostitis.

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Treatment for brachial palsy involves protection of the arm from further trauma and procedures to restore function of the arm.

Intracranial injury is relatively frequent in premature infants, because of their immaturity accompanied by weakness of supporting structures and blood vessels and the tendency to bleed; and the relative frequency of precipitate birth and breech delivery.

Trauma to the head may result in edema of the brain (contusio cerebri) or hemorrhage. The former condition is difficult to differentiate from the latter. Either one may result fatally. In contusion the infants that survive show relatively rapid improvement and complete recovery.

Intracranial hemorrhage is one of the most frequent causes of death of premature infants. The commonest sites of intracranial hemorrhage in premature infants differ from those in full-term infants; that is, intraventricular hemorrhages are the most frequent in the premature infants in contrast to subdural and subarachnoid hemorrhages in mature infants.

The causal mechanisms of intracranial hemorrhage are: molding of the head; sudden lateral compression of the head; forceps extraction through cesarean incisions; abnormal pressure on the head when the membranes rupture prematurely; pressure on the head in breech delivery; precipitate delivery after a short labor. The last three factors play the chief roles in causing intracranial hemorrhage in premature infants.

Diagnosis of intracranial hemorrhage is difficult to make during life. The symptoms are those of increased intracranial pressure which develops rapidly or slowly, depending on the site and extent of the hemorrhage.

Neurologic signs cannot usually be relied on to localize the lesion. Intracranial injury should be suspected when an infant dies sud-

denly shortly after birth or develops labored breathing, cyanosis, twitching, or convulsions. In these cases a massive hemorrhage has probably occurred. With less extensive bleeding these signs develop more gradually after 24 to 48 hours. Lethargy is the predominant symptom and later increased intracranial pressure develops, evidenced by tension of the anterior fontanel.

Intracranial injury must be differentiated from a number of other conditions that occur in the neonatal period. Chief among them are anoxia (asphyxia), septicemia, erythroblastosis, and hemorrhagic disease.

Examination of the cerebrospinal fluid after spinal, ventricular, or cisternal tap should be helpful but the interpretation of findings of blood after spinal tap is difficult. Fresh blood in the fluid may be due to trauma from the needle; yellowish fluid may be evidence, not of decomposed blood but of icterus neonatorum. A strongly positive test for albumin and crenated or broken-down red blood cells in freshly drawn spinal fluid are said to be evidence of true hemorrhage provided a previous spinal tap has not been done. After the early neonatal period neurologic signs may be evident which will clarify the diagnosis. Spasticity resulting from hemorrhage is very difficult to differentiate from that due to congenital cerebral defects.

The treatment of premature infants with intracranial hemorrhage is largely general care—warmth and quiet surroundings, slight elevation of the head, administration of vitamin K and of oxygen, parenteral administration of fluid to meet requirements, small repeated transfusions of blood, and sedatives if indicated by restlessness or convulsions.

There is considerable difference of opinion in regard to the value of withdrawing cerebrospinal fluid to relieve pressure and remove blood. In certain cases it has been found to relieve symptoms. The decision must be made in each case according to the best judgment of the physician. Consideration must be given to the danger of increasing the hemorrhage and, in spinal taps, of herniation of the medulla into the foramen magnum.

Surgical removal, in the early period, of the blood, or later of clots, has been advocated but should only be contemplated in selected cases or in the chronic stage when symptoms of intracranial damage persist and localization of the lesion can be made.

The prognosis for premature infants that survive acute intracranial hemorrhage is obviously poorer than for those who are not thus affected. The prognosis seems to be less grave, however, than might be assumed. In one report 42 of 69 infants that survived intracranial hemorrhage were found on repeated examinations to have no evidence of damage to the central nervous system and their physical growth compared favorably with a control group; 27 showed evidences of damage but only 13 of these were found to be mentally retarded.

Injury to the cord is due usually to stretching of the cord during breech delivery. Although this injury might be expected to occur relatively frequently in premature infants, case reports are rare. It is a very serious type of injury resulting in hemorrhage and tearing or rupture of cord fibers, which is sometimes accompanied by fracture of the vertebrae. In these cases, because of attempts to hasten delivery, direct pressure is also made on the head. Stretching of the cord and pressure on the head favor herniation of the medulla into the foramen magnum.

The diagnostic signs of cord injury are dependent on the site and extent of the injury and the amount of hemorrhage. There may be respiratory difficulties, paralysis of abdominal muscles and legs, and loss of sensation. In the case of respiratory failure from cervical cord injury the diagnosis of death from asphyxia is frequently made without appreciation of the true cause of death. Cord injury is difficult to differentiate from cerebral injury and both lesions may be present in the same infant.

Treatment of infants that survive cord injury is general in the early stages—careful nursing, prevention of further trauma to the spine, and care of the skin. Later orthopedic management is necessary but the chances for complete recovery of paralyzed parts are nil.

Injury to viscera may occur during birth or after birth as the result of attempts to resuscitate the infant.

The liver is the organ most often injured. Rupture of the capsule and hemorrhage may result from pressure of the operator's hands during breech delivery and from pressure on the lower abdomen in attempts to induce respiration after birth. Symptoms frequently do not appear until several days after birth when death occurs suddenly.

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The adrenal glands may also be injured during birth, particularly when in manipulations the infant is grasped around the waist and the trunk is twisted. The lesions are parenchymatous hemorrhage or rupture of the capsule. Death is likely to occur suddenly and unexpectedly. The symptoms are frequently erroneously ascribed to asphyxia or intracranial hemorrhage.

The spleen and kidneys are rarely injured during or after birth.

INFECTION

Premature infants are peculiarly susceptible to infection. Infection may take place in utero, transmitted through the placenta; during birth, from aspiration of infected fluid or from contact with infected maternal vaginal secretions; or after birth as a result of aspiration of oil or other substances, local infection of the cord, trauma to the tissues, or as a contact infection.

Intrauterine infections

GENERAL SEPTICEMIA

Intrauterine infection of the fetus (septicemia) is the result of placental transmission of organisms present in the maternal blood stream. Placental transmission to the infant of tuberculosis, typhoid and paratyphoid fever, malaria, and other infections, as well as syphilis, has been conclusively demonstrated, according to Potter and Adair. Toxoplasmosis is another type of intrauterine infection. Potter and Adair state, however (273, p. 125): "Infections, in comparison to their importance in later life, play a very minor role in causing death of the fetus in utero or of the infant in the early weeks. During fetal life the placenta acts as a fairly effective barrier against bacteria, and this, coupled with the fact that maternal bacteremia rarely exists even in the presence of infection, gives little chance for the fetus to become infected through the blood stream."

It is fortunate that an increasingly large number of infectious conditions transmissible to the fetus are amenable to sulfonamides and antibiotics and that therapy of the mother is effective in the fetus. Speert (332) reported: "Sulfathiazole and sulfadiazine, like sulfanilamide, diffuse readily across the placenta. Following the intravenous administration of a single 5-gm. dose of sodium sulfathiazole or sodium sulfadiazine to the mother during labor these drugs appear in the fetal blood almost immediately and are retained there in therapeutically effective concentrations for at least 6 hours in the case of sulfathiazole and considerably longer in the case of sulfadiazine. . . These drugs appear also in the amniotic fluid but more slowly than in the fetal blood." In Speert's experience absorption of the drug was poor when given orally. No harmful results from this single dose of a sulfonamide in utero were observed in the infants during the neonatal Speert thinks it possible, however, that long-continued sulperiod. fonamide therapy in utero might involve hazard to the fetus.

When the membranes have been ruptured for 12 hours there is special danger of infection and some obstetricians advise giving sulfadiazine or penicillin to the mother to protect the fetus. Penicillin passes

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through the placenta to the fetus in therapeutic concentration, as well as the sulfonamides (161).

SYPHILIS

Syphilis is a form of septicemia which can be prevented by adequate treatment of the mother before as well as during pregnancy. (See p. 20.) If the mother has the disease it will be modified if she receives some treatment during pregnancy. 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. If the infant is not treated until clinical syphilis has developed, the prognosis is more serious than if he is treated earlier.

It is obviously important to determine for an infant born of a syphilitic mother, treated or untreated, whether or not 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 full-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 possible presence of syphilis.

Clinical criteria

One or more of the following clinical signs may be present:

Serous or pustular discharge from nose; fissures around mouth. Macular papular or pustular skin eruption with involvement of

the palms and soles.

Redness and scaliness of palms or soles.

Hemorrhages into the skin and from mucous membranes.

Enlarged spleen.

Tense fontanel, twitching, or convulsions.

None of these criteria is alone pathognomonic of syphilis; the presence of other criteria is required, such as roentgenologic or serologic evidence.

Roentgenograms

Roentgenographic evidences of syphilitic changes in the long bones, unless classical and showing lesions in more than one bone, do not prove the presence of the disease. In fact, skeletal roentgenograms in premature infants require expert interpretation because (1) rapid bone growth and maternal treatment with bismuth alter the appearance of the fetal bone structure, and (2) other diseases bring about changes often misinterpreted as syphilitic. Caffey (59, p. 677) points out: "The reaction of growing bone to syphilitic infection is not unlike that of other chronic infections in many respects. The spirochetes are implanted in the metaphyses and diaphyses and produce destructive and productive changes; in the areas of destruction the marrow cells and bone are replaced by syphilitic granulation tissue. The out-



Figure 27a.

Figures 27 a and b.—Syphilitic metaphysitis in a premature infant one month of age (courtesy John Caffey, M. D., Babies Hospital, New York City).

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Figure 27b.





standing characteristic of infantile syphilis is the multiple bone involvement; in severe cases nearly all of the metaphyses are affected, but in milder cases the changes may be limited to two or three bones, usually the tibias, femurs, and humeri.

"In addition to the local inflammatory changes caused by the spirochetes, trophic changes develop in the metaphyses which are due to the nonspecific generalized effect of a severe disease on endochondral bone formation. These trophic changes are seen at the cartilage-shaft junctions and are responsible for the transverse-band appearance of the metaphyses in roentgenograms. . . . Thickening of the epiphyseal plate and atrophy of the juxta-epiphyseal spongiosa are the anatomic equivalents of the transverse shadows. The transverse-striped appearance of the metaphysis is an almost constant phenomenon in all severe diseases during the fetal period and early infancy; it is not pathognomonic and not diagnostic of syphilis, although almost all patients with active infantile syphilis show some of these trophic metaphyseal changes. Moreover, the administration of bismuth to the mother during pregnancy produces transverse bands of increased and diminished density in the metaphyses of the nonsyphilitic fetus which simulate the trophic transverse striping found in syphilitic fetuses and newborns . . . "

Changes in the bones due to rickets and nonsyphilitic osteomyelitis or osteoperiostitis may also be confused with those due to syphilis. In rapidly growing infants the periosteal shadow is prominent because of inadequate subperiosteal calcification and may be wrongly interpreted as periostitis. Relatively dense shadows at the ends of the bones with rarefaction proximally may be due to rapid growth also.

It is clear that the diagnosis of syphilis from roentgenograms of the bones is difficult unless the lesions are characteristic and multiple at the growing ends of the bones, and there are evidences of bone destruction as well as increased calcium deposition (fig. 27). In cases with such marked bone changes clinical signs of syphilis are usually present also. It is in the cases with no clinical evidences of syphilis that the interpretation of slight roentgenographic changes should be helpful, but unfortunately it is in these cases that there is the greatest difficulty in interpretation.

Serologic diagnosis

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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. Quantitative tests, developed by Faber and Black (100), are helpful in clearing up the significance of these antibodies, as Christie (63) says, possibly before clinical or roentgen manifestations of the disease de-Christie also has shown that in an uninfected infant the titer velop. decreases during the early weeks and eventually becomes negative and remains so; in an infected infant, on the other hand, the titer does not change or it becomes stronger, as is illustrated by two of his cases. In case 1 the infant escaped infection; in case 12 infection occurred. By the fifty-ninth day, when the second infant showed greatly increased titer, he had developed dactylitis, but roentgenograms of the extremities still showed no evidence of syphilis.

	Quantitative Wassermann	
Case 1:	reactions	Units
Maternal blood	44444 <u>4</u> 20	150
Cord blood	4444440	100
Infant's blood :		
7 days	_ 4444420	75
18 days	444200	18
31 days	442000	8
44 days	442000	8
56 days	420000	3
77 days	000000	0
126 days	000000	0
217 days	000000	0
Case 12:		
Maternal blood	442000	8
Cord blood	A422000	8
Infant's blood :		
8 days	A44200	8
31 days	442000	8
45 days	444420	37
59 days	444444420	300

After the second month of life, and in some cases earlier, the infant's specific blood reaction may be considered reliable evidence of intrauterine syphilitic infection.

Treatment

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, or (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.

When the diagnosis of syphilis is established treatment should be begun with due regard to the fact that the welfare of the infant is the primary consideration and treatment of the disease is secondary. Because the infant is premature, (1) special supportive care is needed; (2) the treatment may precipitate gastrointestinal symptoms; (3) complications such as malnutrition, diarrhea, and respiratory-tract infections must be appropriately treated. Supportive treatment consists in maintenance of body fluids and nutrition. When active syphilitic lesions, malnutrition, or respiratory infections are present, repeated small transfusions of whole blood are indicated.

A routine method of treating syphilitic infants with arsenic and heavy metals has been established. The use of penicillin is now being advocated, but penicillin has not been used long enough for dosage to be established nor results of treatment evaluated. Both methods of treatment are therefore outlined.

Treatment with arsenic and heavy metals

An outline for the treatment of the syphilitic infant with arsenic, mercury, and bismuth, as given by Moore (236, p. 506) is shown in table 55.

The results of treatment with arsenic and heavy metals, as reported in the medical literature, evaluated by Whipple and Dunham (393, p. 115) are, in part, as follows:

"The kind of antisyphilitic therapy used must necessarily influence the ultimate clinical outcome. Because of the large number of variables influencing the end results, however, it is not possible to obtain data regarding the most efficacious treatment. The amount and regularity of treatment, the age at which treatment is begun, the severity of the manifestations of syphilis, and the pediatric care of the infants are all perhaps as important as the selection of the drug or drugs used. There is a lack of controlled studies of the effect of different types of treatment.

"The tendency for syphilis to produce clinical signs or symptoms many years after the initial infection has led many syphilologists to give a very guarded prognosis of complete cure of syphilis even in children. Smith (325) has shown that the longer a group of children were under observation the larger was the number of relapses. . . . Relapses were much more frequent in children whose blood Wassermann reactions remained persistently positive than in those whose Wassermann reactions became negative under treatment. The ultimate effect of treatment was found to depend upon the age at which treatment was begun and upon the amount and type of treatment given. Smith (324 and 325) reported that 9 percent of children receiving 'adequate' treatment suffered relapses, compared with 14 percent of those receiving 'inadequate' treatment . . .

"White and Veeder (395) found that when treatment was started before the age of 2 months, 32 percent of the children were 'cured,' compared with 25 percent when treatment was started after the second month but before the second year . . .

"In 13 reports [references omitted] of over 2,000 children diagnosed as syphilitic and treated by well-known methods before the age of 2 years, it was found that only one-fourth of the children were adequately treated and followed long enough to determine the results.

"Fifty-five to 100 percent of clinical and serologic cures are recorded in the various reports on this group, but no constant relation appears between the method of treatment and the percentage of cures.

"It is impossible, considering all the variables in the statistics, to draw any conclusions concerning the relative therapeutic efficiency of the treatment systems used."

Treatment with penicillin

Treatment of the syphilitic infant with penicillin is still in the experimental stage. Dosage has not been established, nor have an adequate number of treated infants been followed over a sufficient period of time to determine results. By analogy with the results of such treatment in adults with acute syphilis there is every reason to think that penicillin treatment, possibly in combination with arsenic and heavy-metal treatment, will replace older methods of treatment of syphilitic infants.

Week	Drug	Dose	Remarks
1 2-7 8-11	Sulpharsphenamine Sulpharsphenamine Mercury (by inunction daily)	5–10 mg./kg 25 mg./kg 1–2 gm	Test blood. Avoid therapeutic shock.
	Bismuth (subsalicylate	2 mg./kg	
12-19	Sulpharsphenamine	25 mg./kg	Test blood. Do not stop treatment when serologic tests become negative.
20–25 26–33	Mercury or bismuth Sulpharsphenamine.	25 mg./kg	Test blood. Also test spinal fluid at about this time.
34-41 42-49	Mercury or bismuth	25 mg./kg	Test blood. Note gradual lengthening of heavy metal courses: 4, 6, 8, and
50-59	Bismuth or mercury		Test blood. This is absolute minimum of treatment, which should be continued longer, if necessary, to fulfill serologic standard. Test blood every 6 months. Test cerebrospinal fluid at end of one year.
Thereafter	Prolong follow-up with ph puberty is passed; and, it	ysical and serologic possible, thereafter a	reexaminations every 6–12 months until at least until early adult life is reached.

TABLE 55 Suggested outline of treatment for early congenital (Moore)

The first report on the use of penicillin in the treatment of infantile congenital syphilis is that of Moore and his coworkers (238). In a review of the status of treatment of early syphilis with penicillin, based in part on army experience, they state: "Not included in the tabular presentations are some 20 infants with early congenital syphilis. The majority of them have been treated with a total dose of penicillin of 20,000 units per kg. of body weight, corresponding to a total dose of 1,200,000 units in the adult. Their behavior in terms of symptomatic improvement and serologic response is analogous to that of early acquired syphilis in the adult."

Subsequent reports of series of syphilitic infants treated with penicillin have been made in the period of 2½ years that has elapsed since the first report. Studies of syphilitic infants treated with penicillin from 1944 to the end of 1946 (196, 262, 397, 166, 150, 243, 406, 296, 263) show favorable results but are based on relatively few cases.

The largest series of cases is that reported in 1947 by Platou and others (264) who pooled the results of a cooperative study made in 5 university clinics. Observations were made on 252 infants (219 Negro, 33 white) under 2 years of age, of whom 44.8 percent were under 3 months of age when treatment was started. The disease was graded as severe in 61.5 percent of the cases and mild in 38.5 percent.

Sodium penicillin in aqueous solution was given intramuscularly in total dosages varying from 770 to 150,000 units per kg. of body weight. Totals of 40,000 units or less per kg. were divided into 60 equal doses and given every 3 hours for $7\frac{1}{2}$ days; larger totals were divided into 120 equal doses and given over a period of 15 days.

The results of treatment with a single course of penicillin administered over a period of $7\frac{1}{2}$ to 15 days yielded satisfactory results in 73.0 percent of the cases; unsatisfactory results, in 9.1 percent; and "uncertain" results, in 17.9 percent.

Better results were obtained when the dosage of penicillin was more than 40,000 units per kg. than when it was less. The authors point I

out, however, that efforts to relate results of treatment to the amount of penicillin given "may be partially invalidated" because "there have been changes in the purity, potency, and composition of commercial penicillin mixtures" furnished since the study began. "There have also been considerable variations in the actual amount of penicillin in individual vials labeled as containing 100,000 units."

"Dramatic clearing of active manifestations of infection" occurred during or soon after treatment. Clinical relapses were infrequent. Most of the infants became seronegative between the fourth and twelfth months after treatment.

Reactions to treatment occurred in less than half the infants, and none were considered severe enough to stop or modify treatment. Aside from transient febrile reactions only 10 infants had "mild or dubious therapeutic shocks."

There were 27 deaths, 9 of which occurred within 14 days after treatment was started. Causes of death other than syphilis were recognized in 22 of the 27 cases; in the other 5 cases information was not available.

Platou and his associates make the following recommendations, to apply "until the true makeup of commercial penicillin has been clarified or until crystalline fractions are evaluated":

- "1. Young syphilitic infants should receive a total dosage of at least 100,000 units per kg. of body weight.
 "2. This amount should be divided into approximately 120
- "2. This amount should be divided into approximately 120 equal intramuscular injections given over a period of 12 to 15 days.
- "3. These injections should be given at intervals of no longer than 3 hours around the clock."

Moore (237, p. 219) has summarized the present status of penicillin therapy in infantile congenital syphilis as follows:

"Much more time is required for final evaluation of penicillin in infantile congenital syphilis, though present information indicates that sodium penicillin in aqueous solution administered every 3 hours day and night, in a total dosage of 40,000-100,000 units per kg. over a period of $7\frac{1}{2}-15$ days, is as satisfactory a method of treatment as has yet been devised.

"The pediatricians concerned have debated among themselves as to whether it is desirable, in an infant who appears critically ill from congenital syphilis and complicating nutritional disorders or associated infections (e. g., bacterial dysentery), to adopt one of three immediate courses to: (a) delay treatment with penicillin until adjunct supportive treatment (fluids for dehydration, transfusion for anemia, restoration of electrolyte balance, and so forth) has improved the general physical status, thus running the risk that the child may die of syphilis before penicillin can be effective; (b) start treatment with penicillin at once in maximal dosage, thus running the risk of a serious and perhaps fatal Herxheimer reaction; or (c) start treatment at once with very small doses of penicillin, building up rapidly to maximal dosage, in order to avoid therapeutic shock. The consensus appears to be that these are matters for individual judgment in each case, but that in general penicillin therapy should be started in maximal dosage as soon as the diagnosis of congenital syphilis is established

Premature Infants

(Herxheimer reactions having been of negligible importance in this material), the usual general medical measures being employed simultaneously.

"Whether penicillin plus some other chemotherapeutic agent (arsenic and/or bismuth) may eventually prove to be more desirable in infantile congenital syphilis than penicillin alone (as seems likely to be the case in acquired early syphilis in adults) cannot yet be determined.

"If retreatment becomes necessary because of clinical or serologic relapse, or of seroresistance persisting for 12 months or more after treatment, it is suggested that the second course approximate that outlined for relapsing early syphilis in adults; i. e., at least twice the original total dose of penicillin plus (in infants) at least 8 weekly intramuscular injections of sulpharsphenamine (15-25 mg. per kg.) and 12 weekly intramuscular injections of bismuth subsalicylate in oil (3-4 mg. per kg.).

"It should be unnecessary to emphasize that congenitally syphilitic infants treated with penicillin be even more vigorously followed for an indefinite period of time than after older forms of treatment, the usual clinical and serologic examinations being repeatedly performed. This is essential until the final status of penicillin is known."

Intrapartum infections

The premature infant may become infected during birth if the mother has a vaginal or enteral infection. The infant's eyes and the vagina may become infected, or the infant may aspirate infected material and develop pneumonia.

EYE INFECTIONS—OPHTHALMIA NEONATORUM

The term ophthalmia neonatorum is applied to several forms of acute conjunctivitis in newborn infants. Gonococcic conjunctivitis, or gonorrheal ophthalmia, formerly the commonest, has been so reduced in incidence by widespread prophylactic measures that inclusion blennorrhea (virus conjunctivitis) is now found more frequently, according to Holt and McIntosh (155, p. 331). Infection of the eye with the pneumococcus, staphylococcus, streptococcus, and other organisms, singly or in combination, may also cause conjunctivitis in the newborn. The newborn infant's eyes may be infected during or immediately after birth or at some time later in the neonatal period.

Gonorrheal ophthalmia

Prevention

Almost all the States (46 in 1945) have laws or regulations requiring prophylactic treatment of the eyes of every newborn infant, specifying the drug to be used and the dosage. Some State health departments provide free of charge for the use of physicians ampules of the drug containing the specified dose.

The general use of prophylactic measures to prevent gonorrheal infection of the newborn infant's eyes during birth has proved to be effective. As a result of widespread use of prophylactics the incidence of blindness from this disease has been greatly reduced. In-

stead of 30 percent as formerly, this disease is now the cause of only 2.4 percent of the reported cases of blindness (370).

The method of preventive treatment used for many years is the Credé method—the use of 1 drop of a 1 percent solution of silver nitrate in each eye immediately after birth. Other solutions of silver salts have been used and are still recommended. Some obstetricians advise flushing the conjunctival sac with a 2 percent boric-acid solution after the use of silver nitrate to avoid irritation of the tissues. The use of salt solution for this purpose has also been advocated but is condemned by some because the salt combines with the chloride to form an insoluble compound and thus tends to minimize the sterilizing effect of the silver.

The instillation of a silver-nitrate solution must be done with care. The drops should be placed in the internal angle of the conjunctival sac after the lower lid has been drawn down.

Lillie (210, p. 1301) states that penicillin and the sulfonamides have proved to be effective agents in preventing gonorrheal ophthalmia, but reports of results of the use of these drugs as prophylactic agents are as yet somewhat meager.

Gonorrheal infection of the eyes of newborn infants still occurs in spite of knowledge of effective prophylactic measures. If maternal infection is not observed or if prophylactic treatment is not done or is improperly done, symptoms of infection of the infant's eyes may be present in the early stages without being noticed.

Symptoms

The term "ophthalmia neonatorum" is applied to infections associated with delivery. In these cases signs of intranatal infection usually appear on the second or third day (always before the fifth day) and are marked by edema and redness of the lids, and discharge that is serous and somewhat bloody at first and then purulent. Delay of treatment even for a day may lead to corneal involvement, with opacity and permanent scarring, or even to perforation of the cornea. Gonorrheal ophthalmia may also be acquired postnatally in the neonatal period.

Diagnosis

Sweet (341) describes as follows the criteria for diagnosis that he used in a study of the disease:

- 1. The clinical finding of a reddened, edematous eye with a severe purulent conjunctival discharge.
- 2. Demonstration of gram-negative intracellular diplococci of typical morphology in the stained films of the eye discharge.
- **3.** In some cases, cultures of the eye discharge for neisseria gonorrhoeae (370). Typical clinical and microscopic findings were accepted as evidence of the disease even when the cultures were negative.

In the early stages of the disease differential diagnosis must be made from inclusion blennorrhea (see p. 252) and from chemical conjunctival irritation due to prophylactic treatment. In the latter the symptoms are not nearly so acute and subside rapidly after irrigations with saline solution. To rule out a gonorrheal infection, however, smears and cultures should be taken.

Treatment

Treatment of gonorrheal ophthalmia with sulfonamides or with penicillin is replacing the old methods of treatment with silver salt solution. Sweet (341) reviewed the literature and also reported treatment with sulfonamides from 1938 to 1941 of 62 patients, among them 48 newborn infants, 13 of whom were premature. Suspected cases were isolated and given general supportive care. The eyes were irrigated with warm boric-acid solution or an 0.8-percent solution of sulfanilamide, and 10-percent argyrol was instilled into the conjunctival sac several times a day, usually one-half hour before the irrigation. (In a personal communication April 1947 Lewis K. Sweet, M. D., Gallinger Municipal Hospital, Washington, D. C., says that he has almost abandoned local treatment of the eyes when sulfadiazine or penicillin is used. He gives only one or two irrigations to wash out the first excess of pus, repeating in the rare cases in which it is necessary.) As soon as the diagnosis was established 0.3 to 0.6 grain per pound of body weight of sulfanilamide (19 infants), sulfapyridine (24 infants), or sulfathiazole (2 infants) was given as an initial dose. followed by a daily maintenance dose of approximately 1.0 grain per pound of body weight given in 6 doses at 4-hour intervals. Three additional infants were given sulfapyridine after sulfanilamide had proved ineffective.

"If the clinical response was not favorable, the dosage of the drugs was increased to 3 or even 5 grains per pound of body weight per day. In a few cases the sodium salt of sulfapyridine was given intravenously to promote a rapid increment of the drug in the blood stream. A 5-percent solution was used; and doses of 0.4 to 0.5 grain per pound body weight were given every 6 to 12 hours as indicated...

"The results of treatment of 62 patients with gonorrheal conjunctivitis are reviewed. Of 30 patients who received sulfanilamide, 24 showed rapid recovery. Thirty-three patients, including 4 who failed to respond to sulfanilamide, received sulfapyridine. A rapid recovery was experienced by 31. Three patients were treated with sulfathiazole; all responded promptly. Only one corneal ulcer developed, this being in a patient on sulfanilamide therapy. Reports on over 45 cases of gonorrheal conjunctivitis treated with sulfapyridine have been collected from the literature. The results in these cases were comparable to those in the current series.

"It is suggested that sulfapyridine is superior to sulfanilamide or any previously used agent in the treatment of gonorrheal conjunctivitis. Sulfathiazole as a therapeutic agent merits further trial."

After study of individual cases Sweet (342, p. 1492) concluded that sulfapyridine, sulfathiazole, and sulfadiazine are all more effective than sulfanilamide in treating acute gonococcus conjunctivitis but that sulfathiazole should not be used because it may be toxic to the conjunctiva.

The effectiveness of penicillin in gonococcus infections has been well established. Sievers, Knott, and Soloway (316) report treatment with penicillin of 8 infants who had gonorrheal ophthalmia (diagnosis definite in 5 cases, probable in 2 and doubtful in 1). The penicillin was given by intramuscular injection at 3-hour intervals "in total dosage varying from 60,000 to 330,000 units." Six of the 8 patients responded promptly, with pronounced clinical improvement within 24 hours and complete recovery in 3 to 6 days. Disappearance of specific organisms in smears and cultures was noted 9 to 24 hours after treatment with penicillin was begun. There were no corneal complications. In 2 infants results were listed as "unsatisfactory."

Sweet finds in his experience that penicillin in a 10,000-unit dose sterilizes the eye in about 3 hours; that four to eight 10,000-unit doses of penicillin will take care of most cases; and that 10 such doses will cure practically 100 percent. (Personal communication from Lewis K. Sweet, M. D., April 1947.)

Lewis (208) reports the results of an 8-year study of the effectiveness of various forms of sulfonamides, as well as 17 months' experience with penicillin, in the treatment of gonococcic conjunctivitis. The diagnosis was established bacteriologically as well as clinically in every case.

Of the 60 patients treated from June 1942 to November 1945, 31 were infants under 1 month of age. These infants were treated systemically—16 with sulfadiazine and 15 with penicillin. "For the past $4\frac{1}{2}$ years local treatment by installation of sodium sulfathiazole, 1 to 5 percent, or penicillin, 500 to 2,500 Oxford units per cc. has been used in addition to the systemic treatment in almost all cases."

With sulfadiazine treatment "clinical cure" of the 16 infants was effected in 2 to 10 days; there was no case of corneal involvement; and there was only 1 recurrence of the infection. With penicillin treatment "clinical cure" was effected in 1 to 5 days, there was no case of corneal involvement, and there was no recurrence of infection. In 2 severe cases sulfadiazine was used in addition to penicillin.

The author concludes that "both the sulfonamides and penicillin are amazingly effective in the treatment of gonococcic infections of the eye." Sulfadiazine is the sulfonamide recommended because it is "quite effective and very well tolerated." Penicillin, however, is regarded by Lewis as even more effective and also as easier to administer to infants.

Lewis (208) outlines as follows the treatment used for infants at the Isolation Hospital in Memphis:

Penicillin: 5,000 units or less at one time. A total of about 100,000 units was usually required to effect a cure in newborn infants.

Sulfadiasine: 0.5 gr. (0.033 gm.) per lb. of body weight for the initial dose, and then 1.0 gr. (0.066 gm.) per lb. of body weight every 24 hours given in divided doses at 4-hour intervals.

The following local treatment is outlined: irrigation of the conjunctival sac every 2 hours with cool boric-acid solution as long as gross pus is visible; after irrigation, instillation of penicillin drops, 1,000 to 2,500 units per cc. of normal saline, every 2 hours; iced compresses for edema of lids and conjunctiva; discontinuance of treatment as soon as the eye is clean clinically and smears are negative; after this, zinc sulfate, 2 gr. (0.13 gm.) per oz. (30 cc.), instilled three or four times a day and continued for about a week after discharge from the hospital. Atropine is used only if there is a corneal involvement.

Lewis (208) presents the following conclusions:

"No toxic, allergic, nor other untoward reactions have occurred from penicillin administration in our series of cases. . . .

"To date we have not felt it justifiable to withhold systemic therapy and rely entirely upon the local use of penicillin in gonococcic

Premature Infants

ophthalmitis, although we feel that its local use is a helpful agent and should be employed . . .

"The systemic use of both penicillin and sulfadiazine is recommended in very severe cases, especially those with corneal involvement . . .

"Penicillin is at present the most effective and the most satisfactory agent for the cure of gonococcic infections of the eye."

Inclusion blennorrhea (virus conjunctivitis)

Inclusion blennorrhea is caused by a filterable virus and, like gonorrheal ophthalmia, is transmitted from the genital tract of the mother during birth. It usually appears later than gonorrheal infection between the fifth and the tenth day. Symptoms are similar to those of gonorrhea, with acute inflammation and copious discharge in the serious cases. Both eyes are usually affected. The cornea does not become involved. Howard (157) says there are no recognizable complications or sequelae.

Diagnosis

Since inclusion blennorrhea is a virus infection, smears and cultures will not show pathogenic organisms unless there is a secondary infection, and this is not common; and repeated negative results, together with the time of appearance of symptoms, should cause inclusion blennorrhea to be suspected. Definite diagnosis is made from scrapings of the lower-lid conjunctiva spread on a slide and stained with Giemsa, which reveal, according to Holt and McIntosh (155, p. 331), "characteristic bluish-granular cytoplasmic inclusions in the epithelial cells."

Treatment

Until the diagnosis is established the infants are isolated, but after that time they can be moved to the cubicles of the regular wards, according to Giddens and Howard (112, p. 340). Local treatment consisting of irrigation of the conjunctival surface with normal saline or boric-acid solution and the use of a mild ointment to prevent adhesion of the lids is suggested by Holt and McIntosh (155, p. 332). With or without treatment the acute stage may last 1 to 2 weeks in the experience of Giddens and Howard (112), and a subacute or chronic stage may last weeks or months; but they report a few cases in which the use of a sulfonamide had shortened the term of the disease. Thygeson (352) also reported that a sulfonamide was effective in causing rapid healing and that the characteristic epithelial-cell inclusions could in no case be found after the third day. In the 6 infants who received what the author regarded as adequate treatment the disease was healed within 2 weeks and there was no recurrence.

Both the sulfonamides and penicillin have been found effective against inclusion blennorrhea, the causative agent being one of the very few viruses that are sensitive to these drugs. The disease is of much shorter duration when they are employed.

VAGINAL INFECTION

Gonococcal vaginitis may be communicated to the infant during birth as well as at any time after birth. The source of infection may be the mother or attendants carrying the causative organisms on their hands. It is rare compared with eye infection but is probably found more often in infants delivered by the breech than in those delivered cephalically. A true specific vaginitis (redness of the mucous membrane and purulent discharge) has to be differentiated from the normal, sometimes copious, white vaginal secretion seen in the early neonatal period. The criteria for laboratory diagnosis are the same as those for diagnosis of this infection in the eyes. If the infection is unsuspected in the mother the diagnosis may be missed in the infant.

The technique for culture of the vaginal secretion for the gonococcus is given by Sweet and Putnam (343) as follows:

"Glass tubes 6 in. long and 5 mm. in diameter are annealed with heat to round the edges. They are sterilized, fitted with a small rubber bulb, and filled for a distance of 2 cm. with warm sterile water. The water acts as a lubricant, and allows the tube to be inserted into the vagina without trauma and to be passed into the vault. Gentle pressure on the bulb washes the vaginal vault and its release draws the washings into the tube. A drop of the vaginal washing is placed on a chocolate agar plate, after which it is spread with a sterile cotton-tipped applicator."

Treatment with the sulfonamides and penicillin has largely replaced other methods and has been found effective, though the optimum dosage and method of administration have not yet been determined. Sweet and Putnam in 1945 considered a dose of 50,000 units of penicillin in multiple injections over a period of 12 hours probably effective for children 7 years old or younger. Sweet now uses a larger amount for infants, 100,000 units in 10 injections, at 3-hour intervals—because of the number of recurrences with the smaller dosage. (Personal communication from Lewis K. Sweet, M. D., April 1947.)

OTHER INTRAPARTUM INFECTIONS

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The premature infant occasionally acquires during birth pulmonary and gastrointestinal infections, the result of aspiration or swallowing of infected secretions of the mother. The symptoms and signs of these infections do not differ except in their earlier onset from those acquired postnatally.

Postnatal infections

The premature infant is peculiarly susceptible to infection after birth. In any newborn infant, as the placental barrier to infection is removed, the portals of infection are multiplied-umbilical cord, skin, respiratory tract, and gastrointestinal tract. The susceptibility peculiar to the premature infant is due to the delicacy of his integumentary tissues (skin and mucous membranes), which makes it easy to injure them; the lack of resistance of an immature organism which, from a sterile environment in utero, is subjected at birth to invasion of organisms; to the low content of gamma globulin in the blood; and to the possible effect of lowered environmental temperatures after birth. Infection may result in general septicemia with or without clinical evidence as to the site of infection. According to Ylppö (409, p. 498), septic infections in premature infants frequently cause death within a few days, "before the typical picture of sepsis shows itself."

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SEPTICEMIA

Any infection acquired by an infant in the neonatal period may result in septicemia. In newborn, especially premature, infants the primary site of infection is usually not obvious and the symptoms are generalized and varied. Ylppö (407, p. 371) pointed out in 1919 that septicemia was an important and relatively frequent cause of morbidity and mortality in the newborn. He reported that in 10 of 14 infants dying between the fourth and the fifteenth day bacteria were demonstrable in the blood stream. Though improvement since that time in obstetric and pediatric technique has undoubtedly reduced the incidence of septicemia, evidence of its continuing occurrence in cases that could not be diagnosed clinically is reported by Dunham (89). She found 39 cases of septicemia in young infants, 9 of whom were premature (birth weights between 1,360 and 2,140 gm.). In all but 1 of the 9 cases the clinical picture was obscure and blood cultures established the diagnosis. In a few postmortem examinations that were per-mitted, conditions found that had not been diagnosed clinically were omphalitis in 2 cases, and peritonitis, secondary to perforation of the stomach, in 1 case.

Ylppö (409, p. 492) states that at postmortem examination numerous small hemorrhages are found especially often in the mucous membrane of the stomach of premature infants. Not infrequently small ulcers may be found in it also. In the intestinal mucous membrane, particularly that of the duodenum, he also found a striking frequency of permeation with blood and often tiny defects. Ylppö considered that these small ulcers might be the origin of a large proportion of the septic processes from which premature infants die. Dunham and Shelton (91) reported the case of a small premature infant who had general septicemia. On postmortem examination multiple small ulcers were found in the mucous membrane of the stomach. organizing thrombi in the umbilical vein and the arterioles of the In this case the ulcers were regarded as the result of thrombi lungs. in the gastric vessels arising from an infection in the umbilical cord.

Diagnosis

Symptoms of sepsis are fever, jaundice, hemorrhage, splenic enlargement, and leucocytosis. Blood cultures should always be made when the diagnosis is obscure, when the mother is ill with an infection, and when there is evidence of local infection in the infant.

Treatment

Treatment consists of (1) maintenance of nutrition; (2) parenteral fluids; (3) blood transfusions; (4) appropriate treatment of local lesions; and (5) treatment with a sulfonamide or penicillin or both, or with streptomycin.

RESPIRATORY-TRACT INFECTION—PNEUMONIA

Premature infants are very susceptible to respiratory-tract infection. Even an upper respiratory tract infection such as otitis media may cause severe general symptoms and lead to a fatal result. The greatest care should be exercised to prevent contact infection (360).

Potter (269) found in her series of 2,000 autopsies on 1,205 stillborn and 795 live-born infants that almost all the nonsyphilitic infections were pneumonia. Though pneumonia was found in stillborn infants, the disease was most common in the live-born infants, among whom there were 124 cases, or an incidence of 15.6 percent. Potter attributed the finding of more pneumonia in this series than in the majority of reports to the fact that lung secretions were examined microscopically in all cases. (She does not discuss the incidence of pneumonia separately for the 503 "previable" and "premature" infants included in table I, p. 996, of her report.) Nelson (247, p. 771) comments on the reduction in the pneumonia case fatality rate among infants that has been effected by sulfonamide therapy.

Pneumonia acquired during birth is the result of aspiration of infected uterine fluid. It occurs most frequently in infants who are suffering from asphyxia and who make respiratory movements during birth. It is more likely to occur, as Potter (269) found in her series, if the mother has early rupture of the membranes, prolonged labor, or other complications of delivery.

Pneumonia acquired after birth may also be the result of aspiration of fluid—milk, vomitus, or cod-liver oil. It may be secondary to some other infection or part of a general septicemia, or it may be a contact infection.

The commoner types of pneumonia are those caused by the pneumococcus, streptococcus, staphylococcus, and H. influenzae and by viruses. In many cases, especially in infants, the pneumonia is due to a combination of bacterial and viral agents or to mechanical injury (aspiration pneumonia) accompanied or followed by a bacterial infection.

According to Adams (5, p. 383), recent research has shown that "the aspiration or gravitation of bacteria-laden exudate plays a more significant role in the inception of pneumonia than does the inhalation of bacteria-containing droplets from the atmosphere. Additional important contributory factors are: (1) immaturity of the lungs, both anatomic and physiologic; (2) lack of neonatal immunity; (3) vitamin-A deficiency; and (4) conditions associated with birth, such as asphyxia." He also comments on "the dual or multiple etiology of many of the pneumonias of infancy," in which "air-borne agents and bacteria-laden exudates play a combined role."

Diagnosis

The infant may or may not show general signs of respiratory infection (such as cyanosis, rapid and labored breathing, and fever). Lung signs, such as impaired percussion note, diminished breath sounds, and rales over a localized area, are often absent or anomalous. The polymorphonuclear leucocyte count usually does not show an increase. Roentgenograms often do not show localized areas of increased density and often are not helpful in establishing the diagnosis. Since the premature infant has little resistance to infection, a blood culture will sometimes be positive, indicating a general septicemia.

Postmortem examination usually shows the pneumonic process to be diffuse. Potter and Adair (273, p. 157) point out: "It is very difficult to make a gross diagnosis of pneumonia in young infants because congestion and hemorrhage of the lungs, especially when these occur in partially atelectatic areas, may produce a similar appearance. The diagnosis must be based on histologic findings." Lipoid pneumonia is due to irritation in the lungs resulting from aspiration of oil. There is no excuse for the development of lipoid pneumonia in young premature infants, for no oil of any kind should be given them orally or nasally (115). (Vitamins A and D should be given in nonoil concentrated form. See pp. 176, 178.) When lipoid pneumonia occurs it is difficult to differentiate by clinical signs from many other types of pneumonia. The symptoms develop relatively late in the neonatal period and may be traceable to a choking or vomiting episode. The original mechanical injury may open the way to bacterial invasion.

Virus pneumonitis or atypical pneumonia to which, according to Adams and his coworkers (6 and 5), premature infants are especially susceptible, may be differentiated from other types by roentgenograms and by its resistance to sulfonamide and penicillin therapy. Like other roentgenograms of newborn infants, these roentgenograms are difficult to interpret. However, in this type of pneumonia evidences of infiltration extending from the hilar regions or diffuse areas of increased density may be found. In infants the disease is commonly associated with secondary bacterial infections. It is extremely contagious. The common symptoms are cough, dyspnea, cyanosis, and low-grade fever. The white blood-cell count tends to be low. Postmortem examination of the infants who died in two epidemics reported on by Adams and his coworkers (6, p. 405) revealed typical cytoplasmic inclusion bodies in the epithelial cells of the bronchial, bronchiolar, and alveolar tissues. Twelve premature infants were included in the study, 10 of whom died, either from the pneumonitis or from associated or subsequent infections (6, p. 419). The average age of the premature infants at onset was 34 days, "a time interval which tends to eliminate immaturity per se (5, p. 379)."

Treatment

The administration of a sulfonamide or penicillin or both is useful in the treatment of most types of pneumonia in a premature infant. The sulfonamides and penicillin differ in their ability to combat different bacterial organisms, though they are both effective against a wide variety. If the infant is in serious condition and if there are complications, penicillin from the beginning is recommended by Albrecht (7, p. 502) because its action is more rapid than that of the sulfonamides. Sulfadiazine and sulfapyridine, according to Davison (78, sec. 126) are the sulfonamides effective against the widest range of bacterial agents and cause the fewest reactions; but if they are used the treatment should be changed to penicillin when improvement does not occur quickly or when unfavorable effects, especially interference with renal function, are noted. Unfavorable reactions from penicillin therapy are relatively infrequent and usually mild. Davison says, in a general discussion of penicillin therapy, that penicillin and sulfonamides together are better than either alone. The combination may therefore be indicated with small premature infants whose initial treatment in most cases cannot wait for determination of the bacterial agent or agents responsible for the pneumonia. Pneumonia usually yields to sulfatherapy and penicillin treatment in 12 to 48 hours, according to Davison (sec. 5). Blood and urine analyses are especially important if sulfonamides are given.

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For premature infants the sulfonamides and penicillin are often administered parenterally. However, Sweet reports that he adds a solution of sodium sulfadiazine to the feeding before it is autoclaved; that the infants take this mixture well and it gives good levels of the sulfadiazine in the blood. (Personal communication from Lewis K. Sweet, M. D., April 1947.) The amount required depends on the severity of the case and the clinical response of the individual infant. Aside from these considerations the dosage for the premature infant follows the recommended dosage for the full-term infant in being based on the infant's weight.

Inhalation of penicillin in concentrated form (penicillin aerosol) has been reported to be effective in treatment of pneumonia, but no report of its use for infants has been found. Knott and Southwell (184) report the experimental use of continuous inhalation of penicillin aerosol by 9 children in oxygen tents. The authors found relatively high concentration of penicillin in the lungs and in the arterial blood during continuous inhalation.

For pneumonia due to H. influenzae or other gram-negative bacilli, streptomycin is used. Sweet says that the dosage has not been worked out but that 25 to 125 mg. every 3 or 4 hours is probably adequate for premature infants. (Personal communication from Lewis K. Sweet, M. D., April 1947.)

In virus pneumonia the treatment is symptomatic. Adams and his coworkers (6, p. 420) concluded after study of 74 infants with pneumonitis: "No specific therapy has as yet been developed for this form of primary virus pneumonitis. General measures, such as the administration of oxygen, postural drainage, aspiration of exudate, blood transfusion, and therapy with the sulfonamide drugs (to combat secondary bacterial infections), have appeared to be efficacious in some cases. Whole adult blood may have prophylactic value, especially in the premature infant."

Supportive care for the premature infant with pneumonia may be outlined as follows on the basis of recommendations by Nelson (247) and Hess (227):

- 1. Avoid "overtreatment," since these feeble infants are unable to withstand overmanipulation or stimulation.
- 2. Surround with warm, fresh air.
- **3.** Administer oxygen continuously, beginning when pneumonia is first suspected. Early administration of oxygen will reduce the need for sedatives and analgesics.
- 4. Administer adequate fluids to promote elimination and to avoid renal complications that sometimes develop with sulfonamide therapy.
- 5. Use cardiac and respiratory stimulants only when indicated. They are not favored as a routine measure.
- 6. Give whole blood intramuscularly every day or every other day. Serum or a small transfusion may be indicated.
- 7. Change the infant's position in bed regularly to avoid discomfort and to facilitate tracheobronchial drainage.
- 8. Give small feedings to aid in preventing distention, vomiting, and diarrhea.

- 9. If there is evidence of distention give prostigmine before it becomes extreme, "especially when it is not relieved by an enema (247)."
- 10. To prevent dehydration or excessive loss of weight give glucose solution between feedings. If fluid cannot be taken by mouth give it subcutaneously once or twice a day in the thighs.

MUCOUS-MEMBRANE AND SKIN INFECTIONS

The premature infant's mucous membranes and skin are especially susceptible to infection because they are very delicate and the slightest abrasion may favor infection. Infections of 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. (See p. 248.)

Thrush

Thrush is oral infection with monilia albicans, a yeast-like organism, which may spread to other parts of the body. The disease may have been transmitted during birth from a maternal vaginal infection, or later through contact with infected infants, contaminated nipples or other equipment, or contaminated hands of the person caring for the infant.

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 if worked at, they bleed. Kolmer and Boerner (186, p. 537) describe their appearance under the microscope as "a tangled network of fine mycelium with clusters of spores. Yeast-like cells are also found laterally along the branches and may lie free." The organism, a fungus, can be identified in smears made from oral swabbing after the addition of a 15 to 20 percent solution of sodium hydroxide. Anderson (23, p. 241) states that "monilia albicans may be present in the oral culture for some time after the lesions of thrush have disappeared."

Treatment

- 1. Cleanse the infant's mouth of mucus with a dry sterile applicator in a rolling motion.
- 2. Dip applicator in 1-percent aqueous solution of gentian violet and roll over mucosal surfaces. Zephiran is also effective.
- 3. At first treat twice a day about 1 hour after feeding; later, one treatment per day.
- 4. Sterilize nipples and bottles used by infant.

Prevention

- 1. Treatment during pregnancy for mothers found to have this infection in the vagina and isolation of their infants until they are proved free of infection.
- 2. Isolation of infants whose oral cultures are positive for M. albicans.
- 3. The scrupulous technique required for prevention of any infection: thorough washing of hands before handling or feeding each infant and careful sterilization, preferably

by autoclaving, of bottles, nipples, and utensils used in preparing feedings. (See 360.)

Umbilical infection (omphalitis)

Infection of the umbilicus may be the result of faulty technique at delivery or in care of the cord during the first days of life.

Diagnosis

Evidences of infection of the umbilicus are redness, moisture, or purulent discharge. The discharge should be cultured, as specific treatment will depend upon the infecting organism. The general symptoms are often slight with little or no fever. Delay in separation of the cord and granuloma of the umbilicus are not in themselves evidences of infection, if the area appears healthy, but delay in separation often occurs in connection with infection.

Erysipelas or general septicemia may develop as the result of umbilical infection. According to Paterson and Bodian (255, p. 256), umbilical infection "may pass to the liver via the umbilical vessels, and as a result liver necrosis accompanied by jaundice and sometimes gastro-enteritis may be present." There is special danger of septicemia in the early days after birth before the cord vessels become firmly thrombosed.

Treatment

The umbilical wound should be cleaned with alcohol and a sterile gauze dressing applied. Systemic therapy—with sulfonamides, penicillin, or streptomycin, depending on the type of infecting organism should be given, together with general supportive treatment. Streptomycin is indicated when the infecting organism is B. coli or other gram-negative bacillus. If there is herniation, strapping during the period of moisture or definite infection of the stump is contraindicated. If the infant is acutely ill or if a positive blood culture is obtained, blood transfusions are called for.

Impetigo neonatorum

Great confusion exists in the terminology of superficial skin infections of newborn infants. The terms impetigo neonatorum, impetigo contagiosa, bullous impetigo, and pemphigus neonatorum are sometimes used interchangeably for simple impetigo. The terms bullous impetigo and pemphigus are more commonly reserved for a more serious infection in which bullous lesions are widely distributed over the body but are not found on the palms and the soles. Whether pemphigus neonatorum is a severe form of impetigo or a separate entity identical with Ritter's disease is unknown. Ritter's disease, starting with hyperemia on the cheeks and spreading over the whole body, is characterized as it progresses by exfoliation of the skin in large sheets.

In its mildest form impetigo consists of small red papules with vesicular or pustular tops, which usually appear in the folds of the neck or other moist or opposing surfaces. The staphylococcus, hemolytic streptococcus, or both, may be found in the lesions. Whether they are the primary cause or are secondary to a virus agent is unknown.

Impetigo is a much dreaded infection that may assume epidemic proportions in hospital nurseries and in its severer forms becomes a

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cause of neonatal death. Because of the delicacy of the skin it is likely to be extensive in premature infants.

Prevention

To prevent impetigo requires aseptic technique in medical and nursing care; sterilization, preferably by autoclaving, of clothing, diapers, and utensils; and avoidance of trauma to the skin, such as may be caused by irritation from rough or wet clothing, by bathing, and by the application of irritating powders or ointments. Infection can take place, however, even if the skin is not broken.

Omission of bathing for the first 10 days to 2 weeks has been found to lower the incidence of impetigo. Smith (326) reports that in a Montreal hospital the incidence of impetigo was about 20 percent between 1942 and 1944, when the practice was to bathe and oil the infants, but that in the 17 months (to January 1946) since bathing of the newborn had been given up and special emphasis put on aseptic technique, there had not been a single case of impetigo among 2,150 infants. Parmelee (254) says there has been only an occasional case in a Chicago hospital during the 7 years in which the combination of no bathing with strict asepsis has been in the practice. (See also Care of the Skin, p. 134.)

Routine inunction with ammoniated-mercury or sulfathiazole ointment has been recommended as a prophylactic measure, but there are definite contraindications to their use for premature infants. Ammoniated mercury has been found to cause skin irritation even in some full-term infants and should not be used for premature infants. The use of sulfathiazole ointment not only causes local reactions in some cases but may sensitize the infant so that he will fail to react to sulfonamide therapy in more serious infections should it later become necessary. The Council on Pharmacy and Chemistry of the American Medical Association (17) has called attention to "the possibility of harmful results following the routine use of suspensions of sulfonamides for the prevention of impetigo in nurseries."

To prevent spread of impetigo in nurseries isolation of suspect cases is necessary.

Diagnosis

In premature infants the diagnosis in the incipient stage, when isolation is most important, is difficult to make. The premature infant's skin is very delicate and therefore susceptible to eruptions on the slightest irritation. Miliaria and dermatitis from soap, oil, or drugs such as ammoniated mercury may simulate the early lesions of impetigo. It must also be differentiated from scabies, diagnosis of which may be confirmed by finding that the mother has scabies. Pemphigus must be differentiated from syphilis and from a rare hereditary skin disease, epidermolysis bullosa. In these two conditions the lesions are multiple and usually are present at birth. In syphilitic pemphigus the lesions commonly appear on the palms and the soles.

Treatment

Treatment of superficial skin infections should be instituted before a definite diagnosis is made. Pending diagnosis these measures should be taken :

- 1. The infant should be isolated.
- 2. All clothing, including diapers, should be removed.

- 3. The infant should not be bathed nor oiled.
- 4. The bed should be kept dry and clean.
- 5. A heat lamp should be used to keep the infant warm and to dry the skin.

After definite diagnosis of impetigo is made the measures outlined should be continued. Various types of local treatment have been used, among them ammoniated-mercury ointment, gentian violet, merthiolate, and zephiran. Ammoniated-mercury ointment has distinct disadvantages in that it may cause skin irritation and may tend to spread the infection, particularly in hot weather. Recently the sulfonamides and penicillin have been used both locally and systemically. The results of treatment with these drugs are shown in the following reports.

Harris (137) reviewed the literature on the treatment of impetigo with sulfonamides and other agents. In the different reports the sulfonamides were administered orally or as an ointment, paste, or powder applied locally. The percentage of cures reported with sulfonamides and other agents was 80 to 100, and the length of time required for a cure varied from a few days to almost a month, the usual time being 10 to 14 days. With microcrystalline sulfathiazole (1 or 2 drops of a 20 percent aqueous solution on a gauze dressing) Harris found that the lesions were healed within 24 hours and no additional lesions developed. The lesions were washed with soap and water and crusts were removed before the sulfathiazole solution was applied. The age range of the 15 children to whom this treatment was given was 1 week to 11 years.

Kendig and Fiske (180) report 14 cases of impetigo in newborn infants treated successfully with freshly made penicillin ointment containing, in 7 cases, 250 units of penicillin and in 7 cases, 333 units per gm. The infants were isolated, the blebs were removed with alcohol on cotton, and the penicillin ointment was then applied to the base of the lesion at least twice daily. No bath was given until the lesions were dry. No new lesions appeared after 48 hours of treatment; all lesions were dry and healed after a maximum of 3 days. Three infants had a recurrence of the impetigo after they had been home from the hospital at least 1 week. The authors point out that although sulfonamide ointment is effective also, "the danger of sensitization of the patient makes its use inadvisable."

Gamble, Miller, and Tainter (108) used the benzyl ester of penicillin dissolved in a strength of 25 mg. per cc. in sesame oil or in propylene glycol in treating impetigo, without removing the crusts prior to treatment. They gave 0.25 cc. (10 drops) by mouth every 4 hours and used no local treatment. They report that this treatment quickly cleared 16 attacks of impetigo contagiosa in 15 infants ranging in age from 3 to 19 days and "terminated a protracted epidemic." Healing occurred in 10 of the cases within 24 hours; there were 3 instances of reinfection in new body areas. No toxic symptoms were noted. The authors consider that the preparation in sesame oil was somewhat more effective. The only other treatment that avoids the necessity of removing the crusts, according to these authors, is parenteral administration of penicillin, which is more difficult than oral administration.

Since January 1944 Aldrich and Holmes (8) have treated all infants who had impetigo neonatorum with intramuscular injections of penicillin, with or without local treatment. Their routine therapy, in addition to immediate isolation, consists of administration of 10,000 units of penicillin in two equal doses 3 hours apart. Local treatment, when given, consists of "applying an antiseptic solution after breaking the blisters and dusting with a powder containing 10 percent mild mercurous chloride U. S. P." Healing occurs promptly, and the infant is returned to the ward within 36 hours.

Pillsbury (261), on the basis of his army experience, considers parenteral administration of penicillin preferable to local application, though simple impetigo ordinarily responds promptly to local penicillin therapy, and local therapy is much simpler and less expensive than injections. However, "the usefulness of topical penicillin therapy in the treatment of superficial infections of the skin is seriously jeopardized by an increased incidence of contact sensitivity which is being encountered. . . Local application of sulfonamides to sites of superficial infection has little or no place in present-day therapy."

Parenteral administration of fluids is important in connection with sulfonamide or penicillin therapy.

Pemphigus and Ritter's disease call for blood transfusions in addition to the treatment given for impetigo. With premature infants the prognosis in these more severe infections is extremely serious. Sweet has found that the vigorous use of penicillin from the earliest possible moment may result in striking improvement. (Personal communication from Lewis K. Sweet, M. D., April 1947.)

Erysipelas

Erysipelas, a streptococcal infection, usually has its origin in cord infection, forceps lacerations, or circumcision wounds. The skin near the portal of infection becomes red, warm to the touch, and edematous, with the extension usually downward. Reuss (290, p. 493) states that in the newborn infant the lesion "does not always exhibit that definite limitation of the diseased area with a sharp, continuously progressing edge, which is so characteristic in the adult." The high fever commonly characteristic of the disease may also be absent in newborn infants, whose temperature may even be subnormal, according to Bradford (47).

"No other disease responds more dramatically to treatment with sulfonamide than does erysipelas (47, p. 390)." The mortality was formerly 70 to 80 percent in neonatal erysipelas, according to Holt and McIntosh (155, p. 124), general septicemia or peritonitis usually developing. With systemic sulfonamide therapy, however, without local treatment, the prognosis is now generally favorable. Roxburgh (298) says that if sulfonamides are contraindicated the infection can usually be cured in 5 or 6 days with penicillin injections. Penicillin may also be used from the beginning. Wrong (404) comments that "results with intramuscular or intravenous administration [of penicillin] are usually extremely rapid and good."

GASTROINTESTINAL-TRACT INFECTIONS

The premature infant is apt to develop vomiting and diarrhea. These symptoms may be evidence of overfeeding, parenteral infection, or enteral infection. In specific enteral infection the stools, if properly cultured, may show the organism responsible. In so-called epidemic diarrhea, one of the commonest of the enteral infections and one of the most serious for premature infants, no organism is found

that might have caused the disease, which has been thought to be the result of virus infection. Some gastrointestinal infections have been associated with infection in the mother, probably communicated to the infant during or after birth.

Specific enteral infections

In regard to specific infections Watt (390) has pointed out some of the difficulties in obtaining satisfactory stool cultures from young infants and of interpreting them. He states that "an outstanding feature of reports on nursery diarrhea is the infrequency with which recognized pathogens have been isolated." (With young infants the rectal-swab technique is more satisfactory than stool culture.) Organisms, usually nonpathogenic, such as paracolon bacilli and pseudomonas, are frequently encountered in the stools of infants in abnormally large numbers, but at this time evidence as to a causative relationship, according to Watt, is "no more than suggestive."

In a nursery for premature infants Watt found three primary infections with recognized pathogens, two with shigellae and one with salmonella, which he considered probably due to infection from the mother at birth; the infants thus infected spread the disease to others in the nursery. He found in another epidemic that pseudomonas aeruginosa (B. pyocyaneus) was probably the causative agent. These organisms were found in large numbers in the stools of the sick infants, and the nursing-nipple container was found contaminated with these organisms, as well as with colon bacilli. The epidemic was controlled by isolation of the infants and proper sterilization of the nursing nipples.

An epidemic of diarrhea occurred among infants born in a Kansas hospital from May to October 1945 (177). There were 24 cases, 17 of which originated in the hospital, and 9 deaths. The age range at death among the 17 infants was 11 to 54 days. Six of the 17 infants were premature and 5 of them died. This epidemic led to an epidemiological study both in the hospital and in the city by the Kansas State Board of Health, which in turn led to the discovery of improperly pasteurized milk as the probable source of the infection and to pseudomonas aeruginosa (B. pyocyaneus) as the responsible organism. This organism was found in the stools of all 9 infants who were studied bacteriologically. All 24 infants were believed to have been infected from mothers, nurses, or other carriers.

Epidemic diarrhea of newborn infants

"Epidemic diarrhea of the newborn is an acute communicable diarrheal disorder of unknown etiology affecting newborn infants in lying-in institutions within the first few weeks of life. It shows a marked infectivity, spreads rapidly from baby to baby, and is characterized by a high death rate (106)." (See also p. 268.)

Clinical signs and symptoms

The first sign of epidemic diarrhea may be the sudden appearance of a loose, watery stool in an infant who has previously appeared well, or the onset may be insidious with such signs as lack of appetite, listlessness, drowsiness, failure to gain or sudden loss of weight and occasional vomiting, and distention. The body temperature is usually nor-

mal or subnormal in the early stages. After the onset of diarrhea the disease progresses rapidly and the infant becomes dehydrated and toxic. Even in this stage the temperature is usually only slightly elevated ($99^{\circ}-101^{\circ}$ F.). The severity of the symptoms varies, however, in different epidemics, as does the mortality rate. High, Anderson, and Nelson (151) reported that they observed in some of the cases a "biphasic" clinical course in which clinical and biochemical improvement was followed in a few days by a more severe attack ending in sudden collapse and usually death.

According to Buddingh (49), "a mild stomatitis or glossitis is present in about three-fourths of cases of diarrhea of the newborn" but is often overlooked. Buddingh and Dodd (50) describe the first local symptoms as fiery redness of the lip and of the anterior margin and under surface of the tongue and the presence of fine vesicles in the affected area. Later desquamation of the mucous membrane of the tongue leaves a raw surface that bleeds readily.

Differential diagnosis

The chief differential clinical signs are sudden onset, relatively low body temperature, severe diarrhea, usually without blood or pus in the stools, and the epidemic character of the disease. In the present state of knowledge it is not possible to make a definite diagnosis unless more than one case occurs.

The diagnosis depends on ruling out, by bacteriologic culture of the stools, other types of diarrheal disease. Frant and Abramson (106, p. 22) state: "To date but little light has been shed on the etiologic agent of the disorder and its portal of entry into the body, nor has the pathway of spread of the infection been determined." So far the results of studies have not been conclusive because in some epidemics bacteriologic studies have been negative and in others various organisms have been isolated that could not be proved to be specific agents of the disease. Lyon (10, p. 685) has pointed out that although "epidemic diarrhea of the newborn may not be a separate and distinct clinical entity," yet the relatively characteristic incubation period "suggests that at times, at least, closely related incitants may be responsible. . . ."

Lyon and Folsom (214, p. 442) reported 15 cases of diarrhea in infants born at a time of unusual incidence of influenza and influenzal pneumonitis. Some of the mothers suffered from "a grippy illness," and 3 critically ill infants showed marked improvement a few hours after administration of citrated whole blood from a patient lately recovered from influenza. To the authors these circumstances suggested the possibility that the influenza virus may be a causative agent in diarrhea of the newborn. High, Anderson, and Nelson (151) were unable to determine the cause of the epidemic that they reported, but they comment: "It may be significant that at approximately the same time there was an outbreak of epidemic diarrhea, nausea, and vomiting of unknown cause in Philadelphia among adults."

Light and Hodes (209) isolated from the stools of infants with epidemic diarrhea in four epidemics occurring in 1942 in Washington and Baltimore a filterable agent that produced diarrhea in 84 out of 85 calves. The agent, not found in the stools of normal infants or normal calves, was not identified. "The evidence suggests, though it is not conclusive, that the agent may be a cause of epidemic diarrhea of the newborn." Buddingh (49) also has isolated from the stools of

infants obtained during 10 epidemics a filterable virus which has not been shown to be the same as that isolated by Light and Hodes, though he says: "When this infection occurs in infants in the nursery, epidemics of the so-called 'diarrhea of the newborn' are prone to develop." Dodd (50, 86), who was associated with Buddingh in the isolation of this virus in cases of stomatitis and diarrhea, suggests that, as in encephalitis, different viruses may be concerned in different epidemics.

Incidence

Statistics on outbreaks of epidemic diarrhea have been kept in New York City (249) since 1934, when the disease was first recognized there (291). During the 11 years ended in 1944 there were 136 outbreaks in 64 hospitals in the city giving maternity care. The number of infants exposed was 15,122 and the number of cases of the disease was 2,302-a morbidity rate of 15.2 percent. Of the 2,302 infants who had the disease 800 died-a case fatality rate of 34.8 percent and a mortality rate of 5.3 percent of the infants exposed to the disease. Some measure of control of deaths from the disease appeared to have been gained, with reduction in the case fatality rate in 1941-43 to 19.2 percent. This was much lower than the 43 percent given by Anderson and Nelson (26) as the average case fatality rate in epidemics at a large number of widely separated institutions, mostly in this country, reported as having occurred from 1928 to 1943. But in 1944 there was a marked increase in New York City both in the number of outbreaks and in the fatality rate (30.1 percent) "traceable in all probability to the wartime strain on hospital facilities caused by overcrowding and the critical shortage of nurses." As a consequence the New York City Department of Health resurveyed the techniques employed in caring for newborn infants and issued new recommendations designed to improve the safeguards for mothers and infants in the maternity hospitals.

A detailed study of an epidemic of diarrhea that occurred in a $10\frac{1}{2}$ month period in 6 San Francisco hospitals was reported by Geiger and Sappington (109). An epidemic was suspected when during 1 month 7 deaths of infants from diarrhea out of 53 known cases were reported to the health department. A survey of hospitals was begun to determine the incidence of diarrhea, and the death certificates were studied and checked with hospital records. There were 324 cases of epidemic diarrhea with 45 deaths, a case fatality rate of 13.9 percent. Of the 42 infants who died for whom information in regard to period of gestation was available on the birth certificates 9 were premature. Geiger and Sappington point out that, in the coding of causes of death, prematurity is given preference over enteritis when the age at death is under 15 days. This means that deaths of very young premature infants, even if they suffered from diarrhea during an epidemic, might be recorded as due to prematurity alone. (See 51, p. 277.)

In 19 outbreaks of epidemic diarrhea among newborn infants in hospitals reported to the Massachusetts Department of Public Health from 1935 to 1945, according to a survey made by Rubenstein and Foley (299), there were 768 infants exposed, 258 cases, and 85 deaths a morbidity rate of 24.6 percent and a case fatality rate of 32.9 percent. In the 19 outbreaks the morbidity rate varied from 10 to 60 percent and the case fatality rate, from zero to 88 percent. Of the 88 premature infants exposed 43 (49 percent) developed the infection and of these 43 infants 23 (53 percent) died. Among the 680 fullterm infants exposed the morbidity rate was 21 percent and the case fatality rate, 25 percent.

Treatment

When the agent is not known, treatment must be, of course, symptomatic and nonspecific. It should be instituted after the first abnormal stool or at the first sign of listlessness and should be directed toward combating the diarrhea and preventing or treating the dehydration and acidosis. Feedings should be discontinued immediately after onset of the disease and resumed very gradually. (See p. 267.) Hydration of the infant should be done by subcutaneous, or in severe cases by intravenous, administration of suitable solutions. Plasma or whole-blood transfusions should be given also.

Whether or not the usual symptoms of acidosis appear Anderson and Nelson (26) consider it important to test the carbon-dioxide combining power of the blood, especially when the disease is becoming more severe, and if the level is low, to correct it by administering alkaline solutions parenterally. They also gave synthetic ascorbic acid and thiamine and amino-acid solution. High, Anderson, and Nelson (151), in a later epidemic in the same hospital, found that neither sulfonamide nor penicillin therapy influenced the clinical course of the epidemic diarrhea though it was of value for combating coexisting infections. Intramuscular injections of gamma globulin were given to some of the infants, but it "had no apparent prophylactic or therapeutic effect." However, the number of infants so treated was regarded as too small to warrant definite conclusions.

Twyman and Horton (359) reported favorable results in the small number of cases that they treated with nonabsorbable succinylsulfathiazole, from its action in altering intestinal flora and its minimal toxicity. Other investigators, however, like High, Anderson, and Nelson, have not found that either chemotherapy or penicillin has any direct effect on the epidemic diarrhea. Dodd (86, p. 705) gives sulfadiazine at first but discontinues it if stool culture shows no dysentery organisms. She gives penicillin only if secondary infection is suspected. The soluble sulfonamides or penicillin may reduce mortality by cutting down bacterial complications, according to Sweet. (Personal communication from Lewis K. Sweet, M. D., Nov. 1947.)

The treatment of epidemic diarrhea at the Cincinnati General Hospital, presented by Dodd (86, p. 705), may be stated briefly as follows:

Parenteral fluid is substituted for oral feeding. Information on electrolytes and osmotic equilibrium is obtained by carbon-dioxide, chloride, and nonprotein-nitrogen determinations. In severely dehydrated infants physiologic saline (50–100 cc.) is administered rapidly. Then acidosis is corrected with 3.7-percent sodium-bicarbonate solution or, if acidosis is moderate, with sodium lactate. "Saline-containing fluids" are given in the first 24 hours in amounts equal to 5 to 10 percent of the body weight in addition to the basal requirement of 100 to 150 cc. of fluid. Five-percent glucose in 100 to 300 cc. amounts is alternated with the saline to make up the 24-hour fluid requirement of 150 cc. per kg. of body weight. Unless severe circulatory collapse or anemia calls for administration of blood or plasma in the first 24 hours, blood, plasma, casein hydrolysates

and hypertonic solutions of glucose or glucose in saline are used only when dehydration is largely overcome. While the diarrhea continues one and a half times or twice the basal amount of electrolyte is given as normal salt solution or the saline in blood and plasma. "The infants are carefully watched for the appearance of edema, the recurrence of diarrhea, and the development of any untoward symptoms. Chemical checks of the chloride, carbondioxide, nonprotein-nitrogen, and protein content of the plasma are made as indications arise." Because hypocalcemia with symptoms of tetany often develops after the acidosis is corrected, the serum calcium is determined if the infant becomes irritable or unduly drowsy, or shows symptoms of collapse or convulsions. As a life-saving measure, calcium is given by such means and in such form that it will be utilized quickly. (For methods of administration see pp. 331, 332.)

On the cessation or marked improvement of the diarrheal condition oral feedings are resumed gradually, beginning with 15 to 30 cc. of water or glucose in water to avoid aspiration pneumonia in case of vomiting, and progressing to gradually increasing amounts of skimmed or half-skimmed milk and sugar. Fluid and electrolyte requirements are made up as necessary by continuing intravenous infusion or by subcutaneous fluids. A tendency to relapse, making it necessary to stop all feedings and start treatment from the beginning, is noted by Dodd (86) as well as by High, Anderson, and Nelson (151).

Dodd (86) also comments that administration of potassium-containing solutions should perhaps be added to the foregoing treatment. Darrow (75) and Govan and Darrow (125) have called attention to the loss of potassium that occurs through dehydration and report strikingly beneficial results from replacement of potassium in cases of severe diarrhea. Potassium-replacement therapy should be undertaken, however, only with precautions outlined by Govan and Darrow, for if the level in the serum is raised beyond a certain point heart block may result.

Intravenous administration of casein hydrolysates (amino acids) calls for very special precautions to avoid infection. The solution is a good culture medium for bacteria, and there may be a systemic reaction to the protein. The danger of infection can be minimized by scrupulous care to avoid contamination by means of a "closed technique," such as was used by Dodd and Rapoport (87). Reactions to parenteral administration of amino acids, according to Bartram (32), "are usually caused by a too rapid rate of injection."

If a hospital is not equipped to make the chemical studies of the blood before and during treatment that are required for the replacement therapy outlined, fluids for subcutaneous and intravenous therapy, such as Ringer's solution or Hartmann's "combined" solution, may be used with fair assurance that the electrolyte balance will not be disturbed. In these cases whole-blood or plasma transfusions also are usually indicated to increase blood volume as well as salt and protein content. Not more than 0.5 gm. of electrolyte per day (plus dextrose solution to make up the fluid requirement) should be given to a premature infant, according to Sweet, because edema results from ingestion of too much salt. (Personal communication from Lewis K. Sweet, M. D., Nov. 1947. See also treatment of acidosis, p. 312.)

Control of epidemic diarrhea

The following measures are essential to the control of epidemic diarrhea:

- 1. Alertness to the appearance of symptoms.
- 2. Complete isolation of suspect cases.
- 3. Report of suspected case to hospital authorities.
- 4. Report of diagnosed case or cases to health department.
- 5. Quarantine of exposed infants by closing the nursery to new admissions.
- 6. Maintenance of rigid isolation technique in care of sick infants.
- 7. Hospitalization of exposed infants during probable incubation period.
- 8. Acceptable technique for cleaning nursery, furniture, and utensils before re-use.

Since control measures include reporting of cases of epidemic diarrhea, it is essential to have a definition of the condition to be reported. In the absence of knowledge of the causative agent the following definition of reportable cases has been recommended (13).

Suspect case. "An infant in the neonatal period who, previously well, suddenly passes one or more very loose or liquid stools combined with sudden abnormal loss of weight (after the period of initial weight loss), or one of the other symptoms associated with this type of diarrhea, such as vomiting, listlessness, drowsiness, refusal of feeding, short, feeble cry, pallor, elevation of temperature, should be immediately isolated and reported to the hospital authorities as a suspect case of infectious diarrhea."

Definitely diagnosed case. "Since there is no definite way of establishing the identity of the disease, the development of similar symptoms in another exposed infant will make it essential to report both the suspect case and the new case to the health department as cases of infectious (so-called epidemic) diarrhea."

New York City makes reportable, regardless of cause, all cases of "diarrhea in the newborn up to 3 weeks of age occurring in a newborn nursery," and the city health department emphasizes the importance of promptness in reporting (249).

Prevention

Since epidemic diarrhea is the result of a hospital infection the cause of which is not known, steps must be taken to avoid every possible source of infection—from the respiratory tracts of attendants, from hand infection, from contaminated clothing, from air contamination, and from the water or milk given to the infants. Having small nursery units in the hospital is very important in the prevention of infection. (For methods of preventing infection of infants in hospitals see **360**.)

The result of inadequacies in these preventive techniques is shown by the report of Rubenstein and Foley (299), who investigated the procedures followed in 10 hospitals in Massachusetts in which out-

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breaks of epidemic diarrhea had occurred between 1935 and 1945. They found that overcrowding, insufficient personnel, general use of a common rectal thermometer, and inadequate supervision of formula making were frequent. "Heavy bacterial contamination" was found in "sterilizing solutions" for hands and thermometers and in formulas, nipples, and utensils. "In several outbreaks apparently identical organisms were isolated from sick and healthy infants, nursery personnel, and formulas." Group D streptococci, normally occurring in the human intestinal tract, were found in the throats of infants with epidemic diarrhea. The fact that several of the outbreaks started among premature infants and spread to full-term infants, these authors comment, emphasizes-the need for particular attention to premature infants in setting up safeguards.

URINARY-TRACT INFECTIONS

Infections of the urinary tract, though frequently referred to as pyelitis, are rarely limited to a single portion of the tract, but involve the renal pelvis and parenchyma (pyelonephritis), the ureters, and the bladder. The incidence of urinary-tract infections is less during the first few weeks of life than in the remainder of the period of infancy. In the neonatal period the incidence is about the same in male and in female infants, according to Rubin (300).

Many organisms may infect the urinary tract, but the colon bacillus is the commonest. Congenital malformations of the tract, which are much more common in male than in female infants, are a frequent cause of infection due to stasis. Urinary-tract infection may also be one aspect of a generalized septicemia.

Symptoms

The symptoms of urinary-tract infection—fever, anorexia, vomiting, diarrhea, convulsions—are not specific. In a premature infant fever may be lacking, and failure to thrive may be the only sign that he is ill.

Diagnosis

On physical examination one or both kidneys may be found enlarged, the causes of obstruction being, according to Davison (78, sec. 147), "inflamed ureter, aberrant vessels, and dilation of the kidney pelvis and calices (hydronephrosis) or abscesses (pyelonephritis)." The ureters and the bladder may be palpable or not, depending on the site of the obstruction. The final diagnosis rests on examination of the urine and on roentgenograms (cystograms or pyelograms).

Urine examinations should be made whenever a premature infant shows any abnormal signs or symptoms. If pus cells are found one should not be satisfied, according to Helmholz (143), with a diagnosis of pyuria. Pus cells in the urine of a female infant may be merely evidence of vaginitis. If they occur in the urine of a male infant a congenital anomaly should be suspected. Cultures should be made to determine the infecting organism, and appropriate steps should be taken to determine whether or not anomalies are present. Determination of the extent and site of urinary-tract involvement entails a complete urologic examination, tests for renal function, and roentgenograms, and is important if the infection persists in spite of treatment.

Treatment

Rubin (300) recommends for children sulfadiazine or sulfathiazole in a dosage of 60 mg. per kg. (½ gr. per lb.) of body weight per day "with quite low blood levels," reduced to 30 mg. per kg. after the first sterile urine is obtained, together with sodium bicarbonate, equal in amount to the sulfonamide, and a high fluid intake. The sulfonamide should be continued until there have been at least three sterile urine cultures at 3-day intervals. This therapy "will control the infections caused by most of the strains of colon bacilli and by many of the other urinary pathogens." A greater concentration of the drug may be needed if the infecting organism is a staphylococcus or a streptococcus. As in all cases in which sulfonamides are used, daily blood and urine levels should be determined in order to provide "satisfactory urinary levels without dangerously high blood levels." (A concentration in the urine of 50 mg. per 100 cc. of urine is adequate, according to Rubin.)

Helmholz (142) studied the effect of various concentrations of streptomycin on the colon bacillus, streptococcus fecalis, pseudomonas aeruginosa, staphylococcus aureus, and other bacteria commonly found in urinary-tract infections. He concluded, in view of the results obtained, that "streptomycin should prove to be the most useful urinary antiseptic so far developed." Herrell and Nichols (146, p. 462) reported that results were considered good in 10 of 13 cases (not premature infants) of moderately severe and severe urinary-tract infection in which streptomycin was administered intramuscularly.

If sulfonamide therapy fails to bring about improvement in a week Sweet recommends that streptomycin be used, after tests have been made for the sensitivity of the organism to this drug. (Personal communication from Lewis K. Sweet, M. D., April 1947.)

It is important in these cases to maintain fluid and nutritional requirements.

(For diagnosis and treatment of congenital malformations of the urinary tract see p. 208.)

OTHER INFECTIONS

Tetanus neonatorum

A striking decrease has occurred in recent years in the neonatal deaths reported to be due to tetanus. Hines (152) called attention to the fact that in the 18-year period, 1910–27, there were 5,767 deaths of infants under 1 month from this disease, an average of 320 per year, whereas in the 5-year period 1938–42 there were only 608 such deaths, an average of 122 per year. In the latter period the neonatal death rate from tetanus remained essentially unchanged, however—0.5 per 10,000 live births. Of all the infant deaths from tetanus 92 percent occurred in the first month of life. Deaths from tetanus among infants under 1 year of age for the 2 years 1943 and 1944 numbered 231, an average of 116 per year, so that the rate for all infants under 1 year (0.4 per 10,000 live births) was lower than the neonatal rate for previous years. Figures for infants under 1 month of age are not available for 1943 and 1944. (52.)

In newborn infants infection with clostridium tetani occurs most often through the umbilicus from contaminated instruments or dressings used at the time the cord is cut. Circumcision, improperly per-

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formed, may also be a source of infection. The tetanus infection is usually not suspected until symptoms appear, and the fatality rate is high regardless of treatment. The disease is, of course, entirely preventable in the newborn infant if aseptic technique is used in cutting and dressing the cord and in performing circumcision.

Symptoms

Symptoms usually appear from 5 to 6 days after birth but may occur earlier. The incubation period is stated to be between 5 and 12 or 14 days but may be as long as 5 weeks. Most characteristic symptoms are convulsions and inability to nurse because of the rigidity of jaw muscles. There may be restlessness, fever, retraction of the head, contraction and stiffness of the muscles of the back, abdomen, and extremities, and twitching of the muscles brought on by the slightest irritation as well as signs of infection of the umbilicus or the penis—redness, edema, or purulent discharge.

Diagnosis

Diagnosis is usually not difficult to make because of the muscle rigidity with marked involvement of the jaws which is pathognomonic. In addition, evidences of local infection and a history of birth or circumcision under unsatisfactory conditions will help to confirm the clinical diagnosis of tetanus. In rare cases it may be necessary to differentiate tetanus from tetany, meningitis, or intracranial hemorrhage.

When symptoms of tetanus have appeared the prognosis is serious at any age and especially serious for the premature infant. The shorter the incubation period the higher the mortality regardless of the treatment.

Treatment

The treatment of tetanus after symptoms have appeared has not been found to be very satisfactory at any age. For infants the principles of treatment, general and specific, are those used for children and adults. These are:

- 1. Quiet surroundings and expert nursing care.
- 2. Use of sedative drugs to relieve muscle spasm and convulsions.
- 3. Maintenance of nutritional and fluid requirements. (See p. 267.)
- 4. Appropriate care of the initial wound.
- 5. Administration of tetanus antitoxin and penicillin.

The infant should be cared for in such a way as to minimize sensory stimuli that excite muscle spasm and convulsions. Sedative drugs, of which there is a wide choice, are also essential.

General rules for the choice of sedative are outlined by Dietrich (85, p. 704) as follows: "The ideal sedative in cases of tetanus should provide rapid and deep sedation without loss of cough and pharyngeal reflexes and with minimal depression of respiration. Further, the drug should be rapidly excreted and of sufficiently low toxicity to permit its continued use in large dosage for considerable periods. Its administration should be possible by other routes than the oral." Dietrich has found in his most recent experience that seconal (so-dium propylmethylcarbinylallylbarbiturate) is a satisfactory sedative

to use in these cases. Silverthorne (317) used it almost exclusively in the cases treated by him "in doses of $\frac{3}{4}$ to 3 grains, depending on the age of the patient and the severity of the spasms." Dietrich (35)found that "even 1 or 2 hours after the administration of 'knockout doses' (i. e., 3 to 4 grains every 3 or 4 hours to a 5-year-old child) it has been possible to arouse the patient to take fluids by mouth." Davison (78, sec. 107) recommends avertin (1.25-percent solution) by rectum in small doses at frequent intervals. Spaeth (330, p. 138) uses sodium amytal and/or avertin with amylene hydrate.

In regard to the specific therapy there is no uniformity of opinion. For local treatment of the wound some authorities advocate surgical extirpation; others consider this undesirable. For example, Weinstein and Wesselhoeft (391) advise, in cases with a single lesion, surgical extirpation of the wound and treatment with an oxidizing agent. They consider that penicillin is strongly indicated in cases "in which no localized area of bacterial invasion can be detected or in which it is impossible to eradicate the focus surgically." Vinnard (367) states that the mortality rate among 11 newborn infants, all of whom had evidence of umbilical-cord infection, "could have been appreciably reduced by routine umbilectomy" in addition to large initial doses of antitoxin (80,000 to 100,000 units). Davison (78, sec. 107), on the other hand, recommends that the wound should be cleaned (debridement and conversion into an open wound) after administration of antitoxin around the wound and by the intramuscular route. Bradford (46) and Dietrich (85) recommend a similar procedure and Silverthorne (317) advocates cleaning of the wound but not ex-Spaeth (330, p. 150) suggests debridement, drainage, and cision. removal of foreign bodies "in the presence of purulent collections"; surgery, if indicated, should be done after sedation and antitoxin therapy.

In regard to systemic therapy it is generally, though not universally, accepted that tetanus antitoxin should be given in all cases. There is considerable difference of opinion, however, in regard to dosage and method of administration, as is shown in table 56. None of the authors specify dosage for newborn full-term or premature infants.

Authority	Total dosage (units)	Method of administration
Davidson (78)	65,000-70,000	Single dose: Intramuscular, 60,000 units; locally around wound, 5,000-10,000 units after a sensitivity test and
Silverthorne (317)	40,000-300,000	Intramuscular. "In the first few days after admis- sion." Dosage dependent upon degree and frequency
Bradford (46)	40,000-80,000	5,000-10,000 locally around wound; remainder divided between intramuscular and intravenous routes and followed by daily intravenous injections of 5,000 units. Initial does preceded by sensitivity test
Vinnard (367) Dietrich (85)	80,000-100,000 10,000-20,000 units a day for 2 to 4 days	Intramuscular and intravenous. Intramuscular. (An initial intravenous dose may be given in savore gesos)
Spaeth (330,'331)	40,000-60,000	Intravenus and intramuscular. The larger dose is for patients admitted during first 5 days; the smaller dose, for "mildly to moderately ill patients first treated later," without regard to body weight.

 TABLE 56
 Dosage and method of administration of tetanus antitoxin according to different authorities

Silverthorne (317) reports on 70 cases of tetanus occurring in infants and children among whom the fatality rate in 1929-35 was 55.5

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Infection

percent and in 1936-46, 28.0 percent. Most of the children ranged in age from 3 to 13 years, but there were 2 infants under 1 month of age. The decreased mortality in the later period is credited by the author largely to the change in recent years from the intravenous to the intramuscular route for injecting the antitoxin, though he mentions occurrence of "a less severe type of illness" in the later years as one of the contributory factors. Dietrich (85) also favors intramuscular administration of antitoxin. Spaeth (331, p. 1160) recommends the intravenous as well as the intramuscular route.

In none of these reports is intrathecal administration of antitoxin advocated. Silverthorne (317), Dietrich (85), and Spaeth (330, p. 143) regard it as unsound and dangerous (or probably dangerous), and Davison (78, sec. 107) and the American Academy of Pediatrics Committee on Therapeutic Procedures for Acute Infectious Diseases and on Biologicals (12, p. 63) advise against it.

In recommending 65,000 to 70,000 units of antitoxin Davison (78, sec. 107) says that the dose should not be repeated, and Spaeth (330, p. 145) also uses a single dose. Davison adds, however, that the administration of "5 daily intradermal injections of 0.1 cc. of fluid tetanus toxoid (undiluted) raises the patients' antitoxin titer." Dietrich (85), as table 56 shows, gives his total dosage over a period of 2 to 4 days, and Silverthorne (317) says his total should be given "in the first few days after admission." Silverthorne speaks of beneficial effects he has observed from repeated doses in some patients whose condition had deteriorated after the initial dose had resulted in a satisfactory blood level.

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Penicillin has been used in the treatment of tetanus, but there are only a few case reports dealing with its use in the treatment of tetanus in infants and children.

Altemeier (9) treated 8 children from 2 to 10 years old with tetanus antitoxin and penicillin and 3 with antitoxin but no penicillin. Of the 8 children who received penicillin 4 died within 60 hours after admission to the hospital. The other 4, who were in the hospital from 4 to 23 days, received 605,000 to 1,560,000 units of penicillin and 50,000 to 250,000 units of antitoxin. Of these children 1 died after being in the hospital 4 days and receiving 605,000 units of penicillin and 100,-000 units of antitoxin. Altemeier concluded that his study failed to show evidence of any beneficial effect of penicillin on the course of the disease. He states that penicillin, although it does exert a definite bacteriostatic effect on clostridium tetani, has no known effect on its toxin, whereas serotherapy does neutralize the free toxin.

Silverthorne (317) administered penicillin to infants with tetanus only when a respiratory infection developed.

Weinstein and Wesselhoeft (391) treated with penicillin and tetanus antitoxin a 4-year-old child who had tetanus. They consider penicillin "a highly important adjuvant," which, however, does not replace other therapeutic measures. The penicillin was administered in doses of 10,000 units every hour by intramuscular drip for 11 days.

Paterson and Bodian (255) treated with antitoxin and penicillin 2 full-term infants 2 weeks and 12 days old, respectively, when tetanus was diagnosed. The infant with the longer incubation period survived, and this infant had received larger doses of antitoxin and penicillin than the one that died. The dose of penicillin was 1,500 units every 4 hours for 14 days, by intravenous drip at first and later by intramuscular injection.

Pratt (278) has reviewed the results of treatment of 56 cases of tetanus in infants and children (5 days to 12 years old) that occurred between 1924 and 1944. When the author arranged the cases in the order of severity and related treatment and outcome to severity it appeared that, with few exceptions, death occurred in the severe cases and recovery in the mild cases, regardless of how much antitoxin was given, or by what route it was given, or what type of sedation was used. These cases antedated the use of penicillin.

Meningitis

Meningitis may occur in rare instances during fetal life. Its incidence is low in the neonatal period also.

In the newborn infant meningitis, according to Anderson (23, p. 239), may be an isolated lesion resulting from "a contiguous focus, as, for example, from an upper-respiratory or ear infection or from an infected meningocele; or it may be one or even the only manifestation of a blood-borne infection."

Syphilitic meningitis is the commonest type in the fetal and neonatal periods. (See p. 242.) In newborn infants, according to Anderson, "the colon bacillus is a relatively frequent cause, as are also the streptococcus, staphylococcus, pneumococcus, and meningococcus." Of 34 cases of purulent meningitis in infants 2 months of age or under collected by Root (295) from published studies, 11 were due to colon bacillus; 9 to staphylococcus and streptococcus; 6 to meningococcus; 4 to pneumococcus; and 1 each to 4 other organisms. Twenty-five of these infants were 1 month old or less. Root reported a case of meningococcic meningitis with a fatal outcome in a 5-week-old infant.

In 386 autopsies on premature infants Hess, Mohr, and Bartelme (149, p. 25) found 10 cases of meningitis, 2 of which were lustic and 8 septic.

Dunham (89, p. 234) reported 39 cases of septicemia (blood cultures positive) in infants in the neonatal period. Meningitis was diagnosed clinically in 6 cases. Cultures of the spinal fluid in these cases showed the following organisms: streptococci, 4 cases; staphylococci, 1 case; mixed culture, pneumococci, staphylococci, and B. coli, 1 case. In all these cases the organisms found in the spinal-fluid cultures were of the same type as those found in the blood cultures. All these infants died. Meningitis was found at postmortem examination in 3 additional cases, 2 due to staphylococci, and 1 to B. coli.

Diagnosis

The clinical diagnosis of meningitis in a premature infant, as in any newborn infant, is difficult because the symptoms are usually vague and atypical until the disease is quite far advanced. Fever is usual but may not be present. Other symptoms are twitching, convulsions, vomiting, and later a tense fontanel and nuchal rigidity.

McKhann (226) has called attention to the difficulty of diagnosis of the disease in infants because of the "bizarre nature of the clinical manifestations. The fulminating type of the disease is uncommon, the presence of petechiae over the body is rare, and the symptoms and signs are seldom those of the classical picture of meningeal involvement." In his series of cases the symptoms were frequently fever,

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vomiting, at times diarrhea, occasionally convulsions. Rigidity of back and neck, though detectable, was "difficult to evaluate in an irritable baby. The Kernig sign was frequently absent. If the fontanel was open it was usually tense or bulging." McKhann (226) considered that "unexplained fever with irritability, bulging fontanel (when the infant was not crying), and variable gastrointestinal symptoms" justified a diagnostic lumbar puncture. Sweet believes that a spinal tap for diagnosis should be done on any infant whose illness is unexplained or whose progress with an infection is unsatisfactory. (Personal communication from Lewis K. Sweet, M. D., April 1947.) Early diagnosis, in spite of its difficulty, is of prime importance. McKhann found that only 4 infants died of the 16 for whom treatment for meningococcic meningitis was begun within a week after the onset of the disease, whereas 21 died of the 23 infants for whom the interval between onset and treatment was longer.

The diagnosis of meningitis can be established, after spinal, ventricular, or cisternal tap, by examination of the fluid, which includes smear, culture, and the use of type-specific diagnostic serums for various organisms.

Purulent meningitis must be differentiated from intracranial hemorrhage, congenital cerebral defect, and various other conditions that cause convulsions.

Treatment

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Treatment must be directed toward the specific causative organism. Specific therapy includes the use of sulfonamides, penicillin, or streptomycin and in some cases therapeutic agents such as specific sera, appropriate to the causative organism. The specific therapy for each type of meningitis differs from that for the treatment of meningitis in older infants and children only in amount of drug or serum given, which is usually calculated in proportion to body weight. For premature infants treatment early in the course of the disease is especially important. General supportive treatment, which involves sedation, conservation of the infant's body heat, and maintenance of fluid and caloric requirements, must be given also. Gavage or parenteral feeding and blood transfusions may be required.

Prognosis

The prognosis has always been poorer for infants, especially those under 1 month of age, than for older children, but it is better now that more effective therapeutic agents are used (45). The improved prognosis for these infants is well illustrated by a case report of Hurst and Astrowe (160).

The infant weighed 5 lb. 3 oz. at birth. On the seventh day after birth a purulent discharge from the umbilicus developed which on culture showed a "nonhemolytic, nonpigment-producing short-chain streptococcus." After treatment with local applications of ethyl alcohol and 10-percent sulfathiazole ointment, and later wet, boric-acid packs and sulfathiazole orally ($\frac{1}{4}$ grain every 4 hours), this infection seemed to be overcome. On the thirty-ninth day of life the infant developed a purulent nasal discharge from which the same organisms were isolated as had been found in the umbilical pus. Parotitis developed. Treatment consisted in two blood transfusions and sulfathiazole orally (at first 1½ grains, then 1 grain, every 4 hours) for 8 days, at which time recovery had taken place. On the forty-eighth day of life the infant developed a nasal discharge again and signs of meningeal irritation. On culture of the spinal fluid the same organism was again obtained. Treatment consisted in administration of sulfathiazole, later changed to sulfapyridine, at first by rectum (because of vomiting) and then orally. On the ninth day the spinal fluid was sterile. A transfusion of blood was given on the ninth day of the meningitis because of increasing anemia. Chemotherapy was continued until the twentieth day of this illness and the infant was discharged as entirely cured 8 days later.

This infant was discharged "entirely cured" on the seventy-sixth day of life, weighing 9 lb. When reexamined at the age of 4 months he showed no residual effects from his illness, was progressing normally, and weighed 12 lb. 2 oz.

There was no report of blood cultures in this case, but it would seem that a general blood-stream infection must have been present. The authors state that the source of infection was the mother, and the portal of entry was the umbilical cord. The mother developed postpartum multiple pelvic abscesses from which the same streptococci were cultured.

The youngest of 9 infants in a series of meningitis cases reported by Ross and Burke (297, p. 748) was 6 weeks of age when admitted to the hospital. No mention is made of weight or maturity. The authors give the following report of this case:

The infant was admitted with a history of fever and diarrhea of 6 days' duration. Several episodes of vomiting and drowsiness occurred 4 days prior to entry. At the time of admission he was critically ill, with marked spasticity, partial opisthotonos, and coarse persistent tremors. The temperature was 104° F. Spinal tap yielded cloudy fluid containing 610 white cells with 93 percent polymorphonuclears; sugar was absent and protein content was 60 mg. percent. Pneumococcus (type 8) was found on smears and culture.

The child received sulfadiazine parenterally (2 to 4 gr. per lb. body weight) and penicillin, both intramuscularly and intrathecally. The intramuscular dose ranged from 30,000 to 50,000units every 2 hours, and a total dose of 14,600,000 units was administered over the course of $41/_2$ weeks during which penicillin therapy was maintained. The intrathecal dose of penicillin was 5,000 units daily, and 16 intrathecal injections were administered for a total of 80,000 units. In addition, 1 cc. of heparin intrathecally was given on 4 consecutive days, when it became apparent that a chronic basilar meningitis was developing. Supportive therapy included parenteral fluids, blood transfusions, oxygen, and sedation for persisting convulsions. No type-specific pneumococcus antiserum was used.

A stormy course in the hospital ensued, punctuated by a complicating urinary tract infection (due to bacillus coli) and persisting diarrhea. The opisthotonos and spasticity gradually disappeared, and after the first week no further convulsive seizures were noted. The spinal fluid became sterile within 5 days after admission and remained so during the remainder of the hospital

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course. The infant was discharged ostensibly well after a 6-week hospital stay. The matter of residual central nervous system damage will have to be determined by future follow-ups.

Summary

Premature infants are peculiarly susceptible to infection, which may occur in utero, during birth, or after birth.

INTRAUTERINE INFECTIONS

Intrauterine infections resulting in general septicemia are relatively rare with the exception of *syphilis*. Sulfonamides and antibiotics given to the infected mother during pregnancy will prevent infection of the fetus in utero provided the drug used is specific for the infecting organism.

Syphilitic infection of the infant in utero can be prevented by early diagnosis and adequate treatment of the mother.

When clinical evidences of syphilis appear, the infant should, of course, be treated at once. In the premature infant clinical signs are rhinitis, first serous, then purulent and bloody; enlarged spleen; macular eruption and redness or scaliness of the palms and soles; and hemorrhages into the skin and from mucous membranes.

Bone changes may be demonstrable by roentgenograms, but early roentgenographic bone changes are difficult to interpret and are not pathognomonic in the absence of other signs of the disease.

The diagnosis of the disease in the infant in the neonatal period, before clinical or roentgenographic signs appear, depends on demonstration of a continued high or rising titer of antibodies in the infant's blood (quantitative test). When these tests are not made the Wassermann test made on the infant's blood cannot be considered reliable for diagnosis until he is 2 to 3 months of age; before that time maternal antibodies transmitted to the infant in utero may be present in the infant's blood without indicating that he is infected.

Treatment of the syphilitic infant should be undertaken with due regard to his nutritional condition and to complications such as diarrhea and respiratory-tract infections. Nutritional and fluid requirements should be met. When malnutrition or any severe active infection is present blood transfusions are indicated.

The method of treatment with arsenic and heavy metals has been established. The effectiveness of the treatment is related to the age at which it is begun and to the amount and type of treatment given. Between 55 and 100 percent of clinical and serologic cures have been reported in children whose treatment was begun before the age of 2 years, but only one-fourth of the children were given adequate treatment and followed for periods long enough to judge results.

Treatment with penicillin is now replacing treatment with these drugs. In a series of 252 syphilitic infants under 2 years of age treated with a single course of penicillin "satisfactory results" were obtained in 73 percent of the cases. The results were better when the dosage of penicillin was more than 40,000 units per kg. than when it was less. The dosage recommended for young infants as a result of this study is 100,000 units per kg. of body weight divided into 120 equal

Premature Infants

doses and given intramuscularly every 3 hours over a period of 12 to 15 days.

According to the consensus of medical opinion, as evaluated by Moore, each case requires individual consideration, but in general, since reactions have been negligible, penicillin should be given in maximum dosage as soon as the diagnosis of syphilis has been established, with simultaneous medical treatment of complications that may be present. If clinical or serologic relapse occurs or the Wassermann tests remain positive 12 months or more, a second course of penicillin treatment is indicated. Moore suggests at least twice the original total dose of penicillin plus at least 8 weekly intramuscular injections of sulfarsphenamine (15-25 mg. per kg.) and 12 weekly intramuscular injections of bismuth subsalicylate in oil (3-4 mg. per kg.).

It is not possible at the present time to give exact data on results of penicillin treatment because insufficient time has elapsed since this treatment was first used and the dosage has not yet been finally established.

INTRAPARTUM INFECTIONS

The premature infant may be infected during birth through contact with infected maternal secretions. The commonest sites for infection of the infant are the eyes and the vagina.

Gonorrheal ophthalmia is preventable by routine installation of a prophylactic in the eyes of the newborn infant. The use of a solution of silver salts, preferably one drop of a 1-percent solution of silver nitrate in the conjunctival sac of each eye, has been found effective. Prophylactic treatment is required by law or regulation in almost all the States.

Gonorrheal ophthalmia presents characteristic symptoms with severe local reaction in the eye—redness, swelling, and serous discharge, later becoming purulent. The final diagnosis depends on demonstration in smears and by culture of the gram-negative intracellular diplococci (neisseria gonorrhoeae).

Treatment should be begun at once, even before the diagnosis is completely established, if permanent damage to the eye is to be prevented. Older methods of treatment with silver salts are being largely replaced by treatment with the sulfonamides and more recently with penicillin. The exact dosages and routes of administration have not been established to the extent that a routine procedure can be outlined at present.

Inclusion blennorrhea is a virus infection which causes symptoms similar to those from gonorrheal infection. Smears made from scrapings of the lids and stained with Giemsa show granular inclusion bodies. Treatment consists in irrigation of the conjunctivae with saline solution and parenteral administration of a sulfonamide or penicillin.

Gonococcal vaginitis may be acquired during birth or after birth from the mother or from attendants carrying the infection on their hands. Local evidence of infection consists in redness of the mucous membranes and a purulent discharge. The criteria for diagnosis are the same as those for diagnosis of this infection in the eyes.

Treatment with a sulfonamide or penicillin is rapidly effective. The exact dosage of neither one of these agents has been established to the point that a routine procedure can be recommended for premature

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infants. One clinic in which relatively large numbers of infants are treated has obtained satisfactory results with penicillin in 10 intramuscular injections of 10,000 units each at 3-hour intervals.

Intrapartum infections of the pulmonary and gastrointestinal tracts of the infant occur occasionally from aspirated or swallowed infected secretions of the mother.

POSTNATAL INFECTIONS

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Premature infants are particularly susceptible to postnatal infections. General septicemia may occur without an obvious primary site or from infections that would be considered mild in a full-term infant. Blood cultures should be made when a premature infant is not doing well and the diagnosis is obscure.

Treatment consists of supportive measures to maintain nutrition and fluid requirements; blood transfusions; appropriate treatment of local lesions; and if the organism is cultured from a local site of infection or from the blood, specific therapy (sulfonamide, penicillin, or both, or streptomycin).

Respiratory-tract infections

Premature infants are very susceptible to respiratory-tract infections. Pneumonia is difficult to diagnose, as symptoms are usually vague and the condition is frequently not recognized during life. Roentgenograms may or may not be helpful in making the diagnosis. Blood cultures should be made to determine the infecting organism.

Pneumonia may be due to one or more specific organisms or may be the result of aspiration of infected material or substances such as cod-liver oil that irritate the lungs (so-called lipoid pneumonia). Premature infants are said to be especially susceptible to an atypical pneumonia, or pneumonitis, of viral origin, which in infants is commonly associated with bacterial infections.

Treatment consists in specific therapy; but since the infecting organism is usually not known at first and prompt treatment is essential, various agents should be tried—penicillin or a sulfonamide or both, or streptomycin if an influenzal pneumonia is suspected. In virus pneumonia the treatment is symptomatic, with penicillin or sulfonamide therapy to combat secondary infections. All types of the disease call for supportive treatment to maintain nutrition and fluid requirements. Parenteral fluid and repeated blood transfusions and administration of oxygen are usually indicated.

Mucous-membrane and skin infections

The premature infant is especially susceptible to infection of the mucous membranes or the skin.

Thrush is evidenced by the appearance of white patches on the mucous membrane of the mouth. The mycelium can be identified in smears after adding 15 to 20 percent sodium-hydroxide solution. Treatment of the condition in premature infants differs in no way from that in older infants except that special care must be taken not to traumatize the delicate membrane when taking material for diagnostic purposes and in applying treatment. Treatment consists in application of an aqueous solution of gentian violet (1-percent solution) or zephiran twice a day at first and later daily.

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Thrush is a preventable condition. Mothers with vaginal thrush should be treated during pregnancy. Isolation of infected infants and aseptic technique will prevent spread of the condition.

Umbilical infection is the result of faulty technique at delivery or in care of the cord in the early neonatal period. Evidences of infection are redness, moisture, or purulent discharge. Cultures of the discharge from the umbilical stump should be made, as specific treatment depends on the infecting organism. General symptoms of infection are usually absent. The wound should be cleansed with alcohol and dressed with sterile gauze. Systemic sulfonamide or antibiotic therapy and supportive treatment, including blood transfusions, should be given. Erysipelas and general septicemia may develop if treatment is delayed or inadequate.

Impetigo is a skin infection that may be very mild (papulovesicular) or very severe (pustular). The severe form (pemphigus), which may be a separate entity related to an exfoliative type of skin disease (Ritter's disease), is characterized by bullae. Impetigo is highly infectious and in its severe form may be fatal to premature infants.

Prevention of impetigo requires aseptic technique and avoidance of trauma to the skin. Omission of bathing for the first 10 days to 2 weeks, together with aseptic technique, has been found effective in preventing impetigo. Routine inunction with antiseptic ointments should be avoided.

Transmission of impetigo can be prevented by isolation of suspect and infected cases, closing of the nursery to new admissions, and thorough cleaning after the incubation period has ended.

General treatment consists in removing clothing and keeping the infant dry and warm with a heat lamp. Various methods of local treatment are advocated. Local application of a sulfonamide or penicillin is reported to be rapidly effective. Rapid healing is also reported through the administration of a sulfonamide or penicillin in various forms, by mouth or parenterally, and with or without accompanying local treatment. The best form of treatment for premature infants and the dosage of various therapeutic agents have not been established.

Premature infants with *erysipelas* do not have the fever and the sharply delimited area of infected skin that are characteristic of this skin infection in children and adults. Edema, redness, and warmth of the skin near the portal of infection (the cord, forceps lacerations, or circumcision wounds) are the chief signs. The infecting organism is the streptococcus, and the response to systemic sulfonamide or penicillin treatment is excellent.

Gastrointestinal-tract infections

Premature infants are prone to vomiting and diarrhea. These symptoms may be evidence of overfeeding or of parenteral or enteral infection.

The diagnosis of specific enteral infections can usually be made by stool culture. The infection may be transmitted from the mother or from attendants who are carriers or whose technique is faulty.

The most dreaded enteral infection is so-called "epidemic diarrhea of the newborn," in which the fatality rate among premature infants is usually high. The cause of this disease has not been determined. Stool cultures have not identified the organism, and there is some evidence pointing to a viral agent.

If epidemics are to be prevented vigilance must be exercised to detect the earliest signs of this disease; to isolate suspect cases; and to quarantine nurseries in which one or more cases of this type of diarrhea occur.

The onset of the disease may be insidious, with general malaise (listlessness, drowsiness, and loss of weight), or sudden, with loose watery stools. The differential diagnosis depends on ruling out by stool cultures specific pathogenic organisms. Numerous outbreaks of this type of epidemic diarrhea have been reported in hospitals widely scattered throughout the United States. The severity of the symptoms, as well as the mortality rate, varies in different epidemics. The case fatality rates reported over an 11-year and a 10-year period were 35 percent and 33 percent, respectively, and the average for a large number of hospitals was 43 percent. In recent years, however, lower rates have been reported—19 and 14 percent. The rates among premature infants have been much higher than among full-term infants.

Treatment of epidemic diarrhea is symptomatic. It should be begun promptly and directed toward combating the diarrhea and preventing dehydration and acidosis. Feedings should be discontinued and resumed very gradually. Blood transfusions should be given. Chemotherapy (succinylsulfathiazole) has been advocated by some authorities, but a number of investigators have found that sulfonamides and penicillin have no direct effect on the course of the disease though both are useful to combat coexisting infections.

The following measures are essential to control the spread of epidemic diarrhea: immediate isolation of suspect cases; report of diagnosed cases to health authorities; quarantine of the nursery; maintenance of rigid isolation technique of care; hospitalization of exposed infants during probable incubation period; cleaning of nursery, furniture, and equipment.

Prevention of epidemic diarrhea depends on following the best standards known for hospital care of newborn infants, including the use of small nursery units.

Urinary-tract infections

Urinary-tract infections in infants are rare in the early neonatal period. The commonest organism found is the colon bacillus, and the commonest cause of infection is stasis due to some congenital malformations of the tract, which occur predominantly in males. The condition may also be one aspect of general septicemia.

In premature infants the only sign of urinary-tract infection may be failure to thrive. Other symptoms of general infection may be present, such as fever, anorexia, vomiting, diarrhea, and convulsions. Physical examination may show that one or both kidneys and the ureters are enlarged. (Normally in premature infants the kidneys may be palpable and lobulations may be felt.) The diagnosis is established by finding pus cells in the urine and by pyelograms. Cultures of the urine should be made to determine the infecting organism.

Specific therapy is directed toward the type of organism found. Sulfonamides and more recently, streptomycin, have been useful in the treatment of the commoner organisms found in urinary-tract infections.

General measures should be taken to maintain nutrition and fluid levels. Surgical correction of some urinary-tract anomalies is possible.

Other infections

The mortality from *tetanus neonatorum* has been greatly reduced in the United States. An average of only 122 neonatal deaths per year has been reported from this cause for 1938–42, compared with 320 per year in 1910–27.

Tetanus neonatorum is entirely preventable. It is usually due to poor technique in care of the cord and during circumcision.

Symptoms are trismus, causing difficulty in nursing; stiffness of the muscles of the back, abdomen, and extremities; fever, retraction of the head, twitching, and convulsions. Signs of infection of the umbilicus or penis may be present. The incubation period varies between 5 days and 5 weeks; the longer the period the better the prognosis. Differential diagnosis must be made from other conditions causing central-nervous-system symptoms. The involvement of the jaw muscles is the chief diagnostic point in favor of tetanus.

The treatment of tetanus at any age is not very satisfactory.

General treatment consists in:

Quiet surroundings and expert nursing care.

Use of sedative drugs, such as seconal, avertin with amylene hydrate, or sodium amytal to relieve muscle spasm and convulsions. The dose is calculated in proportion to body weight.

Maintenance of nutritional and fluid requirements.

Cleansing of the initial wound after local and systemic injections of antitoxin. Some authorities favor surgery.

Tetanus antitoxin, after a skin test for sensitivity to horse serum, should be given intramuscularly—perhaps with an initial dose intravenously—but never intrathecally. The doses of antitoxin recommended vary in different reports and appear to be determined rather by the severity of the attack than by the age of the patient. Total dosages vary between 20,000 and 300,000 units in single doses or in divided doses over a period of several days. Doses as large as 80,000 to 100,000 units have been recommended for newborn infants.

Penicillin has been used in the treatment of tetanus, but there are only a few case reports of its use in infants. It has been suggested that it is an adjuvant to treatment and does not replace other therapeutic measures.

The result of specific treatment of tetanus in infants is difficult to evaluate. The outcome appears to be related to the severity of the disease rather than to the treatment.

Meningitis may result from an isolated lesion such as an ear infection or an infected meningocele, or it may be one manifestation of a general septicemia.

Syphilitic meningitis is the commonest type in newborn infants. Among the purulent meningitides that due to the colon bacillus is one of the most frequent.

Infection

The clinical diagnosis is difficult to make in newborn premature infants since the usual clinical signs of increased intracranial pressure are often not present in the earlier stages of the disease. Tenseness or fullness of the fontanel suggests meningitis, especially if the infant has fever, is irritable, or has a convulsion. In cases with unexplained symptoms or those suggestive of meningeal irritation the spinal fluid should be examined by smear and culture, and by typespecific diagnostic serums for certain organisms. A differential diagnosis from intracranial hemorrhage and congenital cerebral defect can usually then be made.

Treatment of meningitis must be directed toward the causative organism; a sulfonamide or penicillin (or both) or streptomycin, or in some cases a specific serum may be called for. The treatment of premature infants differs from that of older infants and children only in the amount of the drug or serum given, which is usually calculated in proportion to body weight. General supportive treatment is essential: sedation, conservation of body heat, maintenance of nutritional and fluid requirements, and blood transfusions.

In premature infants early diagnosis and immediate treatment are especially important. The prognosis, always poor in these small infants, has been improved by the use of the more effective therapeutic agents now available.

ABNORMAL BLOOD CONDITIONS

Erythroblastosis fetalis

Erythroblastosis fetalis, or hemolytic anemia of newborn infants, is described by Diamond (83, p. 880) as a disease occurring shortly before or shortly after birth and "characterized by excessive destruction of the erythrocytes and by an extensive compensatory overdevelopment of erythropoietic tissue in the bone marrow, the liver, and the spleen, and to a less extent in other tissues. The peripheral blood often reflects this hyperactivity by the presence of numerous nucleated red cells, while anemia develops from the excessive hemolysis. Edema, jaundice, and extreme pallor may be observed either singly or in combination."

In 1932 Diamond, Blackfan, and Baty (84) pointed out that icterus gravis neonatorum, hydrops fetalis (universal edema of the fetus), and congenital hemolytic anemia are different manifestations of a disease occurring at or shortly after birth and characterized by hemolytic anemia in which large numbers of nucleated erythrocytes are present in the peripheral blood. They gave the name erythroblastosis fetalis to the disease, the cause of which was not known.

CAUSE

The syndrome known as erythroblastosis fetalis has now been shown to be the result of a specific blood reaction due to incompatibility of fetal and maternal blood in the Rh factor discovered by Landsteiner and Wiener (193) in 1940; that is, the mother does not have the Rh factor and the infant does, through inheritance from the father.

In the words of Diamond (83, p. 880), "Levine postulated and he as well as other investigators have proved, that in most instances the development of erythroblastosis fœtalis is based upon (1) the immunization of the Rh-negative mother by the Rh-positive red cells of the fetus or, on occasion, by a previous transfusion with Rh-positive blood cells; (2) the production by her [the mother] of an anti-Rh agglutinin; (3) the passage of this soluble substance into the circulation of the infant; and (4) the destruction of fetal erythrocytes after specific reaction with the anti-Rh agglutinin. The result is the development of jaundice, anemia, and all the other signs and symptoms of this disease."

The Rh-negative mother may have been previously sensitized and thus have Rh antibodies in her blood because of one or more intravenous transfusions or intramuscular injections of Rh-positive blood at any time previous to or during pregnancy or by repeated pregnancies with an Rh-positive fetus.

INCIDENCE

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The Rh factor (Rh+) is stated to be present in 85 percent of the white population, 95 to 98 percent of the Negro, and 99.3 percent of the Chinese but in only 58 percent of "pure-blooded Indians" (200)

the Chinese, but in only 58 percent of "pure-blooded Indians" (200). For the white race, on which most studies are based, it has been pointed out (15) that there is an obvious "discrepancy between the relatively large number of marriages of Rh-positive men to Rh-negative women, estimated at about 13 percent of all marriages, and the low incidence of erythroblastosis, namely about 0.1 to 0.2 percent of births. . . ." Diamond (82) reports that his cases show an incidence of 1 in 150 deliveries (0.66 percent). This incidence is also reported by Potter (272) for 1944, when it was higher among her cases than in other years. On the basis of 2,800,000 births in the country in 1944 Potter estimated the total number of infants affected in that year as somewhere between 9,000 and 18,000.

According to Diamond (83), only 50 percent of the pregnancies resulting from mating of an Rh-negative woman with an Rh-positive man will result in an Rh-positive fetus if the man is heterozygous (one Rh-positive and one Rh-negative parent). If the man is homozygous (both parents Rh-positive) the fetus will be Rh-positive in all cases. Development of a mother's sensitization to the Rh factor by pregnancy alone is related to the permeability of the placenta and the number of pregnancies that she has had with an Rh-positive fetus, as well as to her innate ability to be sensitized. Potter (272, p. 118) says: "About 58 percent of Rh-positive men and women are heterozygous; consequently one would expect 71 percent Rh-positive children and 29 percent Rh-negative children in random matings of Rh-negative women and Rh-positive men."

Diamond states: "Because of all these conditions the risk of sensitization by the transplacental route is relatively small, actually about 1 in 20 when the mother is Rh negative and the father and children Rh positive. There hardly seems any reason, therefore, for undue anxiety or forewarning of the Rh-negative woman that pregnancy difficulties and damage to her children are bound to occur if her husband is Rh positive.

"A much more serious danger to the Rh-negative mother results from the transfusion or intramuscular injection of Rh-positive blood cells. . . These start the mechanism of sensitization and antibody production which is subsequently 'boosted' by pregnancies with Rhpositive children. Here the danger is so great that probably 50 to 75 percent of Rh-negative women so treated may become sensitized and have serious difficulties even with a first pregnancy." (Louis K. Diamond, M. D., Children's Hospital, Boston: Notes for address on Rh incompatibility at the American Public Health Association meeting, Nov. 12, 1946.)

According to Potter (272, pp. 126, 128, 133), the incidence of erythroblastosis among Rh-positive infants of Rh-negative women is not more than 1 case in 35 or 40 births. However, the occurrence of erythroblastosis "becomes increasingly likely with each successive pregnancy," and when a woman has once borne an infant with erythroblastosis, all Rh-positive infants that she may bear afterward, no matter how long the intervals, will have the disease. Some women typed as Rh positive give birth to infants who appear to have erythroblastosis, and a very few infants suffering from erythroblastosis are typed as Rh negative at birth. As possible reasons for the seeming occurrence of the disease in some infants of the 5 to 10 percent of mothers who appear to be Rh positive Potter mentions (p. 138):

- 1. Maternal sensitization to:
 - a. One of the Rh subgroups.
 - b. Hr, a rare antigenic substance genetically related to Rh.
 - c. A and B antigens (still not conclusively proved).
- 2. Error in determination of the maternal Rh status.
- 3. Error in diagnosis of the disease.

The typing as Rh negative of a few infants who have erythroblastosis may be due, according to Potter (**p. 143**), (1) to "blocking antibodies that are attached to their blood cells" at birth, in which case, at varying periods after birth, the infants show themselves to be Rh positive, or (2) to testing with standard serum only without differentiation for the Rh subgroups or for Hr and its subgroups.

RELATION OF ERYTHROBLASTOSIS TO ABORTION

Levine and his coworkers (199, p. 321) suggested that Rh incompatibility of the blood of the mother and the fetus may account for some abortions and miscarriages, as a high incidence of abortions and miscarriages has been noted in the histories of mothers of infants with erythroblastosis. Later, however, Schwartz and Levine (312) stated: "Studies of a relatively small series of cases indicate that the Rh factor is important in the production of late but not of early abortions." The fetal age at which isoagglutinins and isohemolysins are present in the blood would obviously be the determining factor. Jones (174) states: "Isoagglutinins have been demonstrated in the blood of a 7 months' fetus." He found also that 78.7 percent of the 197 newborn infants in his study could definitely be placed in one of the four recognized isoagglutination groups. His study, he believed, strongly suggested that all infants can be grouped satisfactorily by testing their cells with known group serums. Isohemolysins were present in 27.3 percent of 121 specimens tested.

According to Diamond, miscarriages before the fifth or sixth month rarely can result from difference in blood type or the action of maternal antibodies on the fetal organism. This is borne out, he says, by tests made in 7,400 miscarriages and abortions. (Personal communication from Louis K. Diamond, M. D., Jan. 1948.) Potter (272, p. 145) considers it "safe to conclude that maternal immunization is seldom a cause of abortion but that abortion may be the cause of immunization. The possibility that hemolytic disease will occur in a first child is greater in a woman who has had an abortion than in one who has never been pregnant."

Hunt (159), after study of the Rh factor in relation to abortion, concluded: "Casual or ordinary abortion seems uninfluenced by the mechanism of the Rh factor. The incidence of stillbirth and neonatal deaths, however, is higher among women who do not possess the Rh factor than among those who do. When recurrent abortion and miscarriage are considered, however, the number of women in a group of 93 whose blood did not contain the Rh factor was somewhat

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higher, comparatively, than would be true in the general population." He found no striking increase in the frequency of abortion or miscarriage after the birth of an infant with erythroblastosis, and a group of 25 women who began to experience abortions and miscarriages after having given birth to a normal child included a smaller proportion of Rh-negative women than is found in the general population. He comments: "The Rh factor possibly has been overemphasized as a cause of abortion and miscarriage at the expense of more common causes, such as dysfunction of the ovaries, pituitary body, thyroid glands, and possibly the testes of the husband. A woman subject to abortion whose blood does not contain the Rh factor deserves a chance to attempt another pregnancy under the more nearly ideal physiologic environment that proper therapy may provide."

DIAGNOSIS

Potter (272, p. 162) regards hemolytic anemia in severe form as "one of the most easily recognized disturbances to which the fetus or newborn infant is subject." But less severe cases presenting only a few of the symptoms may involve difficulty, for "there is no one pathologic change which in itself is diagnostic of hemolytic disease or whose absence excludes the possibility of such a diagnosis."

Clinical signs

The classical symptoms and signs of the disease erythroblastosis fetalis, or hemolytic anemia of the newborn infant, according to Diamond (82, p. 477) are:

- 1. Jaundice within 24 to 48 hours after birth.
- 2. Development of anemia, often at birth but more regularly by the third or fourth day, becoming most profound by the seventh or eighth day if the disease is not of the fulminating type.
- 3. Splenomegaly and hepatomegaly quite frequently present.
- 4. Edema and even universal hydrops noted at or immediately after birth, or within the first day.

In the individual infant one of the three major symptoms, edema, jaundice, or anemia, usually predominates. These major symptoms were formerly the basis for the classification of cases that are now known to be manifestations of the single clinical entity, erythroblastosis. The presence of all three of these major symptoms is evidence of the most severe form of erythroblastosis.

In hydrops fetalis edema is the predominant clinical symptom. The infant is usually stillborn, pale (not jaundiced), and edematous; the amniotic fluid and vernix may be stained a deep-yellow color, and the placenta is commonly edematous. Some live-born infants have a milder degree of edema and survive. Almost all hydropic infants die.

Icterus gravis has a serious prognosis also. In these cases the jaundice is usually present at birth, or shortly afterward, is severe, and persists. There may be yellow staining of the amniotic fluid and vernix also. In the most severe type of icterus gravis, pigmentation and degeneration of the nerve cells, particularly those of the basal ganglia of the brain, occur—a symptom complex known as kernicterus. Infants that survive kernicterus may show spasticity, convulsions, and mental deterioration.

Premature Infants

Sanford and Gerstley (306) have reported a case of severe hemolytic anemia in an infant who, on the ninth day after birth, had an icterus index of 470, which remained at this level until the sixteenth day. This infant did not develop kernicterus but recovered after numerous blood transfusions. The normal icterus index of children and adults is 4 to 6, but that of newborn infants is higher and fluctuates considerably in the first 2 days of life. Bonar (43) reported the average icterus index of 32 nonicteric infants for the first 12 days to be 19.

When anemia is the predominant symptom, pallor occurs, often quite suddenly, within a few days after birth, though it may be masked at first if jaundice is present. The anemia is rapidly progressive. Hemorrhages may occur in the skin or mucous membranes. The jaundice usually present in these cases is less severe than that of icterus gravis. Leonard (197, p. 262) points out that "it is difficult to maintain that anemia is solely or primarily responsible for erythroblastemia. Since jaundice may be present at birth before anemia has developed it seems likely that impairment of liver function exists in these patients." Leonard's study showed impaired ability of the liver to form prothrombin, and the postmortem findings she reported, as well as those of other investigators, showed fatty degeneration and necrosis of the liver.

Laboratory diagnosis

Diamond (83, p. 881) points out: "In the early stages of the disease the outstanding [hematologic] characteristic is the great increase in the number of nucleated erythrocytes in the peripheral blood. In contrast to the premature or full-term infant who for the first 2 days may have from 200 to 2,000 nucleated red cells per cu. mm., the infant with erythroblastosis usually shows from 10,000 to 100,000 nucleated erythrocytes within the first 48 hours of life." According to Diamond, the number of nucleated red cells tends to diminish after this time, and they may even disappear; the erythrocytes decrease very rapidly in the progressive-anemia type of the disease; a persistent macrocytosis is an important diagnostic sign; the number of platelets is low during the first week, and the bleeding time is prolonged; the icterus index is high at birth and increases during the first week.

Although the presence of large numbers of nucleated erythrocytes is suggestive the final diagnosis of hemolytic anemia resulting from Rh incompatibility must rest on finding that the mother's blood is Rh negative while the father's blood and the infant's blood are Rh positive and that anti-Rh agglutinins are present in the mother's serum. In such cases the mother's blood should be tested periodically throughout pregnancy. The demonstration of antibodies early in pregnancy or their appearance during pregnancy with a tendency for the titer to rise is probably evidence that the fetus is Rh positive and in danger of developing erythroblastosis.

Specific tests for detecting Rh antibodies in the blood have been devised which depend for their accuracy on having available human anti-Rh serums of high agglutinin titer, the use of proper technique in making the tests, and sufficient knowledge and experience to interpret the results of tests. In addition to tests for the Rh factor, tests should be made for the international blood groups A, B, AB, and O. In cases in which erythroblastosis occurs in the infants and there is no evidence of Rh incompatibility, tests must be made also for the Hr, M, N, and P blood groups.

It is important that in every community and in every hospital accepting maternity cases, there should be provision for determining the Rh blood type, and an Rh-negative blood bank or known individual Rh-negative donors should be available.

Differential diagnosis

Although, as has been noted, an increase in nucleated red cells is suggestive of erythroblastosis, such an increase may also occur in extremely premature infants and in infants who have congenital malformations of the heart or anoxia from atelectasis or intracranial hemorrhage. According to Diamond (83, p. 882), conditions to be considered in the differential diagnosis are congenital syphilis and other infections, congenital malformations of liver or bile ducts, traumatic or spontaneous hemorrhage with severe anemia and secondary erythroblastosis, and certain primary blood diseases.

Postmortem findings

Leonard (197) has reported the findings at postmortem examination in 17 cases of so-called hemolytic disease of the newborn. "All showed extramedullary hematopoiesis, invariably in the liver, almost constantly in the spleen, and frequently in the kidneys, adrenals, pancreas, and thymus. Five patients had hemorrhages of sufficient severity to account for death, either intracranial or gastrointestinal. Eight others exhibited hemorrhages of lesser magnitude. Two infants died of infection: one of the urinary tract; the other, a hemolytic Staphylococcus aureus septicemia secondary to aspiration pneumonia. The cause of death was not obvious in the other patients. Many had varying degrees of atelectasis and/or bronchopneumonia. Five had cardiac hypertrophy. Nine showed necrosis, fatty degeneration, or unusual pigmentation of the liver. Four had small areas of hemorrhage or necrosis in the adrenals. One showed slight hypertrophy of the islets of Langerhans. Five had kernicterus, one of which was severe."

The postmortem findings in the liver of four premature infants, as reported by Leonard (p. 258), are shown in table 57.

TABLE 57Postmortem findings in the livers of four premature infants who
died of hemolytic anemia (Leonard)

	Age at death	Weight (gm.)	Liver
Case 11	3 days	2, 460	133 gm.; pale, extensive fatty degeneration; congestion;
Case 13	do	2,080	72 gm.; large areas necrosis; usual foci hematopoiesis.
Case 20	4 days	2, 220	88 gm.; pigment granules, large amount hematopoietic tissue.
Case 49	5 minutes	2, 250	118 gm.; hematopoietic foci one-half bulk of liver.

TREATMENT AND PROGNOSIS

Infants with mild symptoms of erythroblastosis, such as slight jaundice or slight anemia, often recover spontaneously. In more severe cases the only specific treatment is repeated transfusion with Rh-

Premature Infants

negative blood. Blood from the mother should not be used. Leonard recommends 20 cc. of whole citrated blood per kg. (9 cc. per lb.) of body weight injected into a superficial vein at a rate of 5 to 20 cc. per minute.

Diamond (83, p. 883) says: "Early transfusion of properly matched whole blood or washed red cells is imperative and should be repeated, as necessary, to maintain the infant's blood at a satisfactorily functioning level until normal hematopoiesis begins. . . . Intramuscular injection of blood is not satisfactory." In cases in which the pregnant woman has had one or more previous pregnancies resulting disastrously because of Rh sensitivity, treatment of the infant immediately after birth is probably indicated. Harville (140) has reported the successful use of cord transfusion of Rh-negative blood in a case of this kind involving also delivery by cesarean section 30 days before term.

In very severe cases in which signs of erythroblastosis are present at or shortly after birth Diamond recommends replacement trans-(Notes for an address on Rh incompatibility at the American fusion. Public Health Association meeting, Nov. 12, 1946.) Wallerstein (371) also recommends "substitution transfusion" immediately after birth in cases in which the maternal history and serologic and genetic data indicate the likelihood of severe erythroblastosis in the infant with probable impairment of hepatic function and kernicterus. One of his cases was a premature infant weighing 2,013 gm. (4 lb. 7 oz.), delivered by cesarean section at 38 weeks' gestation, whose mother had an extremely bad previous history, including 1 infant who had died of erythroblastosis. The substitution transfusion, removing 165 cc. of blood and replacing it with 225 cc. of Rh-negative blood, was begun 27 minutes after birth and completed in 37 minutes. The infant was discharged from the hospital in good condition on the sixteenth day.

In addition to transfusions, general supportive treatment for dehydration and maintenance of body temperature, and appropriate feeding should of course be given.

Leonard (197) points out that treatment of the mother or infant with vitamin K is indicated, although the effect on the prothrombin level of the infant is often slight or delayed because of poor liver function. She suggests that the administration of vitamin K to Rhnegative donors before withdrawal of blood might be beneficial. She also states that for the infant a high-protein, high-carbohydrate, lowfat diet, as well as liver extract and choline, warrants further trial.

The sensitized Rh-negative mother of an Rh-positive infant should not be allowed to nurse her infant in the first few days after birth because her breast milk may contain agglutinins. Rh antibodies have been demonstrated in breast milk as late as the fifth day in a sufficiently high titer (1:16) to agglutinate the breast-fed infant's Rh-positive cells, according to Witebsky and Heide (400).

The prognosis in these cases varies with the maturity of the infant, the severity of the symptoms, and the age at which the symptoms appear. The clinical evidences may be so slight that the condition may not be diagnosed unless it is suspected because of the maternal history. When marked edema is present, or when early, very marked jaundice occurs, the prognosis is serious regardless of treatment.

Severe icterus (icterus gravis) may damage the nuclei in the brain and result in spastic paraplegia, mental retardation, and other signs of cerebral nerve damage. Other complications are cardiac failure, hemorrhage, and liver dysfunction. All these complications, Diamond points out, occur in the first 5 or 6 days after birth when the infant suffers from severe antibody-antigen reaction, and it is in this period that proper treatment is essential. "After the fifth to sixth day the infant with erythroblastosis who has suffered no serious internal injuries will usually make a good recovery. If severe anemia develops, even as late as the second week of life, it is easily treated by proper blood transfusions. The recovery after the first week is slow but almost always certain. There may be a period of relatively poor blood production, and multiple transfusions may be required as long as the third or fourth week of life. but usually not beyond this period. No evidence of later difficulty in blood production or blood destruction has been encountered in any of the many hundred cases followed by us." (Louis K. Diamond, M. D.: Notes for address on Rh incompatibility at the American Public Health Association meeting, Nov. 12, 1946.)

Potter (271) states that among 19,000 infants born at the Chicago Lying-In Hospital during a $5\frac{1}{2}$ -year period 30 deaths and 20 stillbirths were believed to be due to erythroblastosis, "making the incidence of fatal cases approximately 1 in 380 births."

PREVENTION

1

Levine (198) enumerates the following methods for the prevention of erythroblastosis:

- 1. Prevent the isoimmunization of the Rh-negative female population that results from transfusion with Rh-positive blood.
- 2. Recommend that an Rh-negative mother should have no further pregnancy until at least a year after all residual agglutinins have disappeared from her blood.
- 3. Test the blood of the pregnant Rh-negative woman periodically to detect the earliest onset of isoimmunization. (If antibodies are present and on the increase the physician can make the diagnosis of fetal erythroblastosis well in advance of delivery.) In selected cases labor can then be induced prematurely to shorten the period of intrauterine hemolysis, though the value of this procedure has not yet been determined.

There is absolutely no known way of "desensitizing" an Rh-negative woman who has become sensitized to the Rh factor nor of preventing her from being more highly sensitized by a future Rh-positive fetus.

Diamond recommends in cases where the mother's antibodies are powerful, that the infant be delivered "2 to 4 weeks before term, depending on the size of the infant and the ease with which it can be delivered," and considers "rupturing the membranes under sterile precaution and initiating labor by medicinal means shortly thereafter" a suitable procedure. He says: "No proof has yet been advanced that cesarean section improves the chances of survival of an infant with hemolytic anemia." (Louis K. Diamond, M. D.: Notes for address on Rh incompatibility at the American Public Health Association meeting, Nov. 12, 1946.) Boorman and her coworkers (44) made repeated Rh tests of a consecutive series of 2,000 mothers during pregnancy and in the puerperium and Rh tests of their infants. They comment: "In view of the possibility of finding a solution to the problem of hemolytic disease, we feel that the practice of some form of birth control would be preferable to the sterilization of an Rh-negative woman with a history of this disease among her children, especially if she is young. It should also be borne in mind that circumstances might arise in which she might have normal infants by another husband who was Rh negative or Rh positive of the heterozygous type."

Potter and Willson (275) suggest that in some cases artificial insemination from an Rh-negative donor is indicated as a means of preventing erythroblastosis. They give the following illustrative case:

A woman whose first pregnancy resulted in the birth of a normal infant had two subsequent pregnancies that resulted disastrously. After the last of these, the third pregnancy, it was discovered that the mother's blood was A, Rh negative, her husband's O, Rh positive, and the infants (twins), both of whom died, showed evidence of erythroblastosis. One year later this woman was artificially inseminated with semen from an Rh-negative man. She gave birth to a normal infant whose blood was A, Rh negative.

Hemorrhagic disease

It is now well established that hemorrhagic disease is associated with an exaggeration of a physiologic hypoprothrombinemia which occurs in all newborn infants within the first 2 or 3 days after birth and from which recovery is usually spontaneous at the end of the first 7 to 10 days.

The following definition of hemorrhagic disease was proposed by Clifford (11, p. 660) at a round-table discussion of the American Academy of Pediatrics on hemorrhage in the newborn infant: "Hemorrhagic disease is the syndrome of spontaneous external or internal hemorrhage accompanied by hypoprothrombinemia occurring in the newborn, excluding that associated with trauma, asphyxia, or some definite disease."

INCIDENCE

Hemorrhagic disease is said to occur more frequently in premature than in full-term infants. The reported incidence of this condition varies considerably, largely because of lack of agreement as to definition. Waddell (**368**) cites reports in which the incidence of hemorrhagic disease varied from 0.03 to 0.5 percent (3 cases, or 0.03 percent, in a series of 9,000 births reported by Sanford; 0.3 to 0.5 percent, by Clifford; 32 cases, or 0.05 percent, among 6,290 infants reported by Waddell in reviewing the records at the University of Virginia Hospital; Waddell included in his figures only cases that showed a prolonged clotting time). Javert (**170**) reported in 1938 the incidence of hemorrhagic disease as 0.773 percent (62 cases) among 8,019 infants born in the "indoor service" of the Woman's Clinic of New York Hospital, and 0.304 percent (10 cases) among 3,284 cases in the "outdoor service." Reports on incidence of the disease when vitamin K is given prophylactically to mother or infant are discussed under prevention (p. 295).

CAUSES

I

The physiologic changes in the blood after birth that lead to prolongation of the clotting time have long been known. As early as 1913 Whipple (394) suggested that the underlying factor was the prothrombin essential to blood clotting. According to Warner (389), "the only known effect of vitamin K upon the economy of the animal organism is in the maintenance of the prothrombin of the blood," which "apparently is produced in the liver. . . In the absence of an adequate amount of vitamin K the prothrombin falls even though the liver is functionally intact." This vitamin, which, as it occurs naturally, is fat-soluble, is believed to be made available for prothrombin production through synthesis in the intestine (so far as premature infants are concerned food sources are negligible) and absorption with the aid of bile salts.

The decrease in the prothrombin level of the infant's blood after birth has been attributed to failure to receive sufficient vitamin K in utero to maintain the level during the early postnatal period, when the bacterial flora essential for synthesis of the vitamin in the infant's intestinal tract have not yet been established. Among premature infants other possible factors mentioned by Levine (202) are faulty absorption from the intestinal tract due to an inadequate supply of bile salts or to poor fat absorption, and inefficient utilization of the vitamin by the immature liver.

Hemorrhagic disease occurs when the hypoprothrombinemia is extreme. However, the two conditions are not always associated. Anderson (23, p. 247) says: "Because of the lack of complete consistency between the tendency to hemorrhage and the prothrombin level of the blood, it is generally conceded that there must be a second, as yet unexplained, factor which is operative."

DIAGNOSIS

Clinical signs

Bleeding, internal or external, occurring during the first week of life may be a sign of hemorrhagic disease, though it may also be of traumatic or septic origin. It may occur in the gastrointestinal tract (melena neonatorum), from the umbilicus, or into the skin and subcutaneous tissues, or less frequently from the nose, mouth, or urinary tract or in the central nervous system.

Laboratory diagnosis

If laboratory tests also show hypoprothrombinemia when bleeding is present the diagnosis of hemorrhagic disease is definite. If there is bleeding but the prothrombin time is normal Snelling (11, p. 659) believes that the diagnosis of hemorrhagic disease cannot be made. As many infants, however, have a low prothrombin time without bleeding, he suggests the possibility, also mentioned by Anderson, that another factor initiates the bleeding. Poncher and Kato (268) regarded the prolongation of prothrombin time without hemorrhage as "subclinical hypoprothrombinemia," differing only in degree from the clinical type with hemorrhage.

Prothrombin tests

A number of methods of determining the prothrombin content of the blood are in use. A simple method, devised by Quick (280) and modified by other investigators, is practical and sufficiently accurate, and a micromodification of this method, originally developed by Kato (178) with later modifications, is especially applicable to infants. The micromethod is described by Warner (389) as follows: "...

The micromethod is described by Warner (389) as follows: "... a drop of fresh capillary blood [is] obtained from a small stab wound. The first drop of blood is wiped away to avoid contamination with an excessive amount of tissue juice. With the aid of a micropipette 25 cu. mm. of blood is then quickly drawn and added to 5 cu. mm. of thromboplastin solution, previously placed upon a clean glass slide. The blood and thromboplastin are mixed by stirring with a small glass rod and the clotting time is noted. The results obtained with this microadaptation of the 'bedside' method are quite satisfactory for clinical use. With the small amount of blood used for the test chilling of the blood quickly occurs and the clotting time is slightly longer than that obtained with the test-tube method. For this reason it is important that the determinations on the unknown and control bloods are made at the same room temperature.

"A number of thromboplastin preparations are available commercially. Any of these appear to give satisfactory results providing the activity of the thromboplastin solution is sufficient that the clotting time obtained with normal blood is not greater than 40 seconds.

"The prothrombin activity can . . . be expressed in percent of normal by the simple calculation:

 $\frac{\text{Clotting time of control (sec.)}}{\text{Clotting time of unknown (sec.)}} \times 100 = \frac{\text{prothrombin activity in per$ $cent of normal"}}{\text{cent of normal"}}$

The normal infant's "prothrombin activity" (clotting time in percentage of normal) is given by Davison (78, sec. 179) as 100 percent at birth, 40 to 50 percent at 2 to 3 days, and 80 to 100 percent at the tenth day, whereas in premature infants the clotting time fluctuates. Bleeding usually occurs in infants, he says, when prothrombin activity is less than 20 percent, and in hemorrhagic disease of the newborn the percentage often falls below 5. The evidence in reports of prothrombin levels in the blood of premature infants compared with full-term infants, according to Potter (270), "suggests that premature infants are more subject to abnormalities of prothrombin time . . ., but this has not been definitely proved."

Differential diagnosis

A number of conditions cause bleeding in the neonatal period. The commonest of these, other than hypoprothrombinemia, are birth trauma, syphilis and other blood-stream infections, and severe jaundice due to congenital biliary anomalies.

The differentiation of so-called hemorrhagic disease from hemorrhage due to birth trauma has long been a matter of controversy. Obviously an infant who has hypoprothrombinemia will bleed more readily when trauma occurs. Prevention of hypoprothrombinemia, however, will not prevent hemorrhage from birth trauma when actual rupture of blood vessels occurs, although administration of vitamin K may tend to control the degree of hemorrhage when small vessels are involved.

TREATMENT

The treatment of hemorrhagic disease with vitamin K has been well established on a clinical basis. Poncher and Kato (268) treated 22 infants with hemorrhagic disease by means of synthetic preparations of vitamin K. The infants were found to have "typical clinical manifestations of bleeding" prior to treatment: hematemesis (16 cases), melena (8 cases), omphalorrhagia (8 cases), dermal or cutaneous hemorrhage (3 cases), cerebral symptoms (3 cases), and hematuria (2 cases). In 12 cases two or three of these symptoms occurred in the same infant. The average prothrombin time (micromethod of Kato) in 10 cases before treatment was 210 seconds (range 110 to 272 seconds); in 12 cases it was prolonged beyond 5 minutes. The age range at onset of symptoms was 24 to 96 hours. The authors give 43.2 seconds as the average prothrombin time on the first day of life found by the micromethod for normal mature infants and 46.5 seconds for premature infants, these values decreasing to the normal 25 seconds by the sixth to the tenth day of life.

Poncher and Kato (268) treated all these infants with vitamin K (fat-soluble and water-soluble preparations). They state that "the average prothrombin time for all cases during the 24 hours following treatment was reduced to 26 seconds" (range 20-34 seconds). No blood was given in these cases. "In all cases the clinical improvement was both prompt and permanent, and the therapeutic effects of the several vitamin preparations used were practically identical."

Snelling $(32\hat{s})$ points out: "Vitamin K by mouth [to infants] may not be retained or absorbed, so it is not safe to use this as the sole source of treatment. Intravenous synthetic vitamin K will lower the prothrombin time and arrest bleeding in hemorrhagic disease of the newborn infant. If the hemoglobin is low, transfusion should be used in addition."

In the pediatric department of the New York Hospital hemorrhagic disease of the newborn (and sometimes bleeding of which the cause is obscure) is treated with 2 mg. of a "water-soluble vitamin-K-like substance," repeated in 24 or 48 hours if indicated. In addition, transfusions with "the freshest available blood, preferably at once," are advised (250). When transfusions are indicated, 10 to 20 cc. per kg. of body weight (41/2-9 cc. per lb.) of whole fresh compatible blood (matched for usual groups and for the Rh factor) should be given once a day for 2 or 3 days until evidences of bleeding cease and the prothrombin time becomes normal (100 percent adult normal).

PREVENTION

Investigators agree that the physiologic fall in the prothrombin level of the infant's blood in the neonatal period can be prevented by administration of vitamin K to the mother during pregnancy or labor or to the infant after birth. Whether administration of vitamin K prevents hemorrhagic disease cannot be determined from the studies so far available, which have yielded widely varying results.

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Clifford (11, p. 659) reported in 1942 that among 1,023 cases given prophylactic vitamin K there was no hemorrhagic disease, whereas among 1,945 controls there were 7 cases (0.35 percent). Waddell (368, p. 658) at that time also reported that with prophylactic administration of vitamin K hemorrhage other than that due to trauma had become "negligible." In 1945 Waddell and Whitehead (369) said that there had been no cases of hemorrhagic disease among more than 4,000 infants born at the University of Virginia Hospital who had received vitamin-K prophylaxis, though the previous incidence had been 0.3 percent. In their definition, however, they include both spontaneous hemorrhage and "hemorrhage precipitated by trauma" when the hemorrhage is associated with prothrombin deficiency and prolonged clotting time.

Several studies of all types of hemorrhage in the newborn, however, led the investigators to different conclusions. Sanford and his associates (307) reported after a study of 1,693 newborn infants that hemorrhagic manifestations "occurred in about equal numbers ... whether the prothrombin value of the blood was low or high or whether the infants or their mothers were given vitamin K or not." They believed, however, that none of these infants "suffered from hemorrhagic disease of the newborn . . . because their coagulation values were within normal limits," although, according to Clifford's definition, the incidence in their series would have been 0.8 percent. Parks and Sweet (253) reported the incidence of severe hemorrhage to be about three times as high among premature infants as among full-term infants, but "there was no significant statistical difference in the percentage of hemorrhage occurring in treated and untreated full-term and in treated and untreated premature infants," though the vitamin K was effective in raising blood prothrombin levels. Among more than 13,000 infants studied, approximately half of whose mothers received vitamin K, Potter (270) found only 2 cases that might possibly be classified as hemorrhagic disease if this disease is considered to be "unrelated to trauma, anoxia, or other pathologic state." These 2 infants died on the second and third day, respectively. In one case the mother, and in the other case the infant, had been given vitamin K.

Waddell and Whitehead (369), who believe that vitamin K decreases the incidence of hemorrhagic disease, and Sanford and his associates (307) and Potter (270), who found no evidence of such decrease, agree that prophylactic administration of vitamin K has not lowered neonatal mortality rates. Lehmann (195), however, reported from Göteborg, Sweden, that deaths from all types of hemorrhage between the second and the eighth day among 17,740 full-term infants from 1934 to 1940, when no vitamin K was given, numbered 34, compared with 6 among 13,250 full-term infants in 1940-43, when vitamin K was given. He considers this difference statistically significant and calculates that the routine administration of vitamin K saved 1.6 full-term infants per 1,000 so treated.

In view of the conflicting evidence and the high incidence of hemorrhage among premature infants it seems wise, in order to be on the safe side, to give vitamin K to pregnant women and to all premature infants.

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The prophylactic doses of vitamin K recommended by Hellman are as follows:

To the pregnant woman.—During the last 2 weeks of pregnancy, one 1-mg. tablet per day. ("This could well be extended to the last 2 months . . . in view of the possibility of premature labor.") On admission in labor or shortly before labor, if previously untreated, 4.8 mg. intramuscularly, repeated every 24 hours until delivery.

To the premature infant.-2.4 mg. intramuscularly in all cases.

(Personal communications from L. M. Hellman, M. D., Department of Obstetrics, Johns Hopkins Hospital, Oct. 8, 1947, and Nov. 10, 1947.)

Anemia

Premature infants, like all newborn infants, tend to develop an anemia beginning in the early neonatal period, which is probably physiologic, like that of full-term infants. However, the symptoms in premature infants are usually more pronounced and persist longer than those in full-term infants, and their severity is directly proportional to the degree of prematurity. Recovery from this type of anemia is usually spontaneous in premature infants, as it is in fullterm infants, though severity of the anemia, especially in the presence of complications, may make treatment necessary or desirable.

In the second or third month of life premature infants tend to develop an anemia that is due to iron deficiency. This type of anemia responds to specific therapy. If iron therapy is begun at about 6 weeks it tends to modify or prevent the development of this type of anemia.

These are the most frequent types of anemia to which premature infants are subject and the only types that will be discussed. Like full-term infants, however, premature infants may suffer from many other types of anemia and careful differential diagnosis is essential.

NEONATAL ANEMIA

To understand the early anemia it is necessary to understand the characteristics of the blood of the premature infant at birth and in the neonatal period. These are in part an expression of immaturity and in part physiologic and probably comparable to those of full-term infants in the neonatal period. Many immature cells of all types are in the blood at birth—more in the premature than in the full-term infant—and they may be found for several months. The erythrocyte and hemoglobin levels, high at birth, fall from about the second week until the eighth to the twelfth week of life, and then tend to rise again until they attain normal levels by the seventh or eighth month. This process is more pronounced in premature infants than in full-term infants and is greater the greater the degree of prematurity, according to Blackfan and Diamond (**36**, **p. 26**).

Exceptionally low levels or failure to return to normal within a reasonable time must be considered evidence of some pathologic process and not of prematurity per se. The normal course was reported by Blackfan and Diamond to be followed, even in infants weighing as little as 900 gm. at birth, when weight gain was steady, but they found that the anemia might be prolonged when associated with nutritional disturbances, infections, or congenital anomalies.



Figures 28 a and b.—Red blood cell counts and hemoglobin levels in infants, from birth to 13 weeks of age. Group I is composed of those babies whose cords were tied promptly after birth; group II is composed of those whose cords were allowed to stop pulsating before being tied (courtesy of Aldula R. Johnson, University of Colorad School of Medicine).

Cause

What causes the blood constituents of the premature infant to be different from those of the full-term infant? The differences have been ascribed to various factors: (1) deficient antenatal storage of iron or some other essential hematogenic material; (2) deficient blood for-

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mation due to marrow hypoplasia; (3) greater blood destruction; (4) more rapid growth and consequently greater demand for blood placed on a more immature and probably less actively functioning hematopoietic system; (5) smaller total blood volume at birth, resulting in a limited supply of substances reutilized for hemoglobin formation. In addition, it has been found that if the circulation in the umbilical cord is interrupted by clamping before pulsation has ceased, the infant does not get the full complement of placental blood.

That deficient antenatal storage of iron, copper, and probably other essential material is not primarily responsible for the early anemia of prematurity is now generally accepted (14). Some authorities hold that this anemia results from increased blood destruction, the amount of hemoglobin at birth being greater than is needed in view

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of the increased oxygen saturation of the blood after birth. Others believe that the rapid increase in body mass and in blood volume exceeds the rate at which red-blood cells and hemoglobin are produced and thus results in dilution of the blood. In newborn infants the red blood cell count and the hemoglobin level are higher if clamping of the cord is delayed until after pulsation ceases. The differences are shown in figure 28. This delay would seem to be particularly important for premature infants.

The erythrocyte counts of 75 premature infants in three birthweight groups, by age, studied by Blackfan and Diamond (36, p. 28), show that:

- 1. The fall in erythrocyte level in the first 3 months is much greater than that found in the normal full-term infant.
- 2. The degree of anemia is directly related to the immaturity of the infant, which is roughly proportional to the weight or length at birth, the smallest infants developing the most profound anemia.
- 3. The lowest level is reached about the third month.
- 4. A return to normal occurs by the seventh or eighth month if the infant is well.

Blackfan and Diamond (36, pp. 27-29) state that "at the twelfth week the hemoglobin concentration is always lower, proportionately, than the number of erythrocytes. Thereafter it rises much more slowly than the erythrocyte count," as is shown in figure 29a. Figure 29b shows that the degree of anemia, as judged by erythrocyte counts, is directly proportional to the degree of prematurity, as shown by birth weight.

Blackfan and Diamond also found that the cellular characteristics of the erythrocytes show little or no change from normal; that "the leukocytes usually follow the normal variation for age in number and type" except for lymphocytosis; that leukopenia occasionally occurs from the second to the fifth month; and that the platelets do not differ from normal in number or character.

Diagnosis

According to Blackfan and Diamond, the principal clinical sign of the early anemia in premature infants is pallor of the skin and mucous membranes, which develops gradually and may not be noticeable until some time in the second month of life, then increases to the end of the third month, and decreases until the color becomes normal about the seventh month. This anemia, they say, does not affect appetite, physical activity, temperature, or stools; there is no bleeding and no noticeable enlargement of the superficial lymph nodes or the liver, but the spleen may become palpable.

Serial determinations of the erythrocyte counts and hemoglobin concentration, begun shortly after birth, show the characteristic course of the early anemia in premature infants—a sharp downward trend in the first 10 to 12 weeks. (See fig. 29.)

The anemia of prematurity needs to be distinguished, according to Diamond (83, p. 869), from the anemia resulting from acute pyogenic infections, syphilis, and specific blood diseases. (See Infection, p. 241, and Erythroblastosis, p. 284.)



Figures 29a and b.—Anemia of prematurity (from Blackfan, Kenneth D.; and Diamond, Louis K.: Atlas of the Blood in Children. New York: Commonwealth Fund, 1944).

(a) Erythrocyte and hemoglobin levels of an infant born 2 months before term. He weighed 2 lb. 12 oz. at birth and his length was 16½ in. Note the rapid fall in blood levels to the tenth to twelfth week, then spontaneous recovery in the ensuing 4 months. The hemoglobin concentration lagged behind the erythrocyte count during this recovery period. (b) See page 302.

Treatment and prevention

Abt and Nagel (2) found that, in the prevention of early anemia in healthy premature infants, iron alone was of doubtful value. In addition, neither desiccated hog stomach nor liver fraction alone proved of value; each was given to 3 infants. When tested on a group of 13 premature infants favorable results seem to have been obtained when a combination of dried-liver fraction and iron in the form of ferrous ammonium citrate (1 to 2 gm. twice daily, increased to 4 gm. twice daily, mixed with a small amount of milk mixture and given at the end of a feeding) was started in the second week of life. The response to this medication was most marked in the infants of 6 to 7 months' gestation, in whom the anemia was the most severe.

Merritt and Davidson (230, p. 301) report: "Premature infants treated with iron or liver and iron after they became anemic showed a greater decline of erythrocytes and hemoglobin and responded more slowly to treatment than did those who received antianemic therapy from birth. . . In the majority of premature infants a more or less severe anemia develops. . . This anemia cannot be entirely prevented, but it can be ameliorated by the early administration of iron in large doses."



(b) Composite graphs of 75 prematurely born infants divided into three groups according to birth weight. In the prematurely born infant the fall in erythrocyte level during the first 3 months is much greater than the normal "physiologic" anemia of the full-time infant. The anemia is directly related to the degree of prematurity or immaturity of the infant, which is roughly proportional to the weight or length at birth; the smallest infants develop the most profound anemia. The lowest level is reached by about the third month, and improvement thereafter produces a return to normal levels by the seventh to eighth month if the infant is otherwise well.

Magnusson (217, Supp. 1, 1935, p. 48) treated with ferrous chloride 29 premature infants weighing at birth 1,000 to 2,500 gm., from the ninth day of life to the age of 6 months. They showed the usual fall in hemoglobin up to the twelfth week, but subsequently the level was significantly higher than in the untreated infants.

From study of 62 premature infants for the first 3 or 4 months of life Josephs (175, p. 1256) concludes: "There was a period of failure to react to the administration of iron that lasted from 6 to 10 weeks after birth, the duration of the period depending largely on the degree of prematurity. After this early period of nonreactivity there followed a short transition period with delayed response, after which administration of iron was followed by a prompt response of the reticulocytes and a rise in red cells and hemoglobin. . . . Although iron may raise the hemoglobin content, transfusion must still remain the method of choice in treating the condition as a whole." The author found no evidence that liver is necessary as an adjunct to iron; both iron and liver were ineffective in the early period, but given later each was effective; copper had no demonstrable effect.

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Mackay (215) studied during the first 6 months of life the hemoglobin level of the blood of 150 infants, of whom 39 infants weighed less than 5 lb. at birth and 52 weighed between 5 and 6 lb. Some of these infants were given an intramuscular injection of 15 cc. of human blood with 1 cc. of 1-percent citrate solution within the first 3 days of life. Since this treatment did not appear to influence the hemoglobin levels, the results of iron therapy (iron and ammonium citrate, usually $4\frac{1}{2} - 6\frac{3}{4}$ grains daily), started before the infants were 45 days old and continued to the age of 26 weeks, were analyzed. When the lowest average hemoglobin levels of infants thus treated were compared with those of untreated infants (all infants in both groups weighing less than 6 lb.), there was a difference of less than 1 percent, and the lowest figure in both groups occurred in the fourteenth week ot life.

Mackay found that the hemoglobin level of none of the infants weighing less than 5 lb. at birth fell below 63 percent (10+gm.) in the first 6 months of life. "The 3 and 4 pounders started with a higher haemoglobin level than the 5 pounders, but from the 8th day until the 22d [week] were consistently slightly lower than the bigger babies. Babies showing symptoms of any severe pathological condition in the early weeks of life were excluded from these groups."

Though investigators differ as to the value of attempting to prevent or treat the early anemia of prematurity, Sanford (305) and Anderson (24), who have recently reviewed the subject, agree that this anemia is not prevented by the early administration of iron but that especially severe cases require treatment. If the hemoglobin has dropped below 60 percent (10 gm.) by the second week of life Sanford (p. 27) gives 3 drops of 50-percent iron and ammonium-citrate mixture in each of the six feedings and increases the dose to 5 drops per feeding at 4 weeks of age if there have been no digestive upsets, which, he says, almost never occur. If the hemoglobin falls below 50 percent (8 gm.) he gives a transfusion of 50 cc. of citrated whole blood.

Anderson also considers transfusions the most effective treatment in very severe cases, especially those associated with infection. She suggests two or three intravenous transfusions of properly typed and cross-matched blood, each consisting of 10 cc. of blood per lb. of body weight, with administration of ferrous sulfate or ferrous gluconate for the infant who has reached 5 lb. in weight as supportive treatment and as prophylaxis against iron-deficiency anemia. (See p. 304.) Before the infant has reached 5 lb., Anderson considers that the administration of iron is usually ineffective and may interfere with feeding. She adds, however, that although the infant may be able to overcome the anemia of prematurity without specific therapy, "it is generally observed that untreated infants are more susceptible to infection and do not have as satisfactory progress in growth and development."

Diamond (83, pp. 869–870) thinks that transfusion is seldom necessary except in the presence of complications. Though he mentions the belief of some writers that "early treatment with antianemic measures . . . does lessen the degree of the anemia," his own conclusion is that "therapeutic efforts to correct or halt the development of the physiologic anemia of prematurity within the first 3 months of life for the most part have been unsuccessful." However, he suggests that "after the third month of life and during the recovery period, since **Premature Infants**

restoration of the hemoglobin level lags behind that of the erythrocytes," it may be of value to give 2 to 4 grains daily of ferrous sulfate or other preparation of iron.

Premature infants who are taking iron may develop diarrhea. In this case the iron should be reduced in amount or temporarily discontinued.

IRON-DEFICIENCY ANEMIA

An anemia due to iron deficiency is common in the second half-year of infancy. Among premature infants, especially those of very low birth weight, it is likely to develop considerably earlier and to be more severe unless prophylactic iron has been given, starting at 6 weeks to 3 months of age. The anemia is frequently associated with infection, to which premature infants are peculiarly liable, and in such cases, Cooley (68, p. 12) comments, "anemia lowers the resistance to infection and infection aggravates the anemia."

Cause

Iron-deficiency anemia in the premature infant, like the earlier type, is associated with immaturity of the hematopoietic system. Moreover, the premature infant's relatively low store of iron at birth (perhaps especially low if the mother had anemia) combined with the rapid rate of growth leads to early depletion of the supply of iron available for building hemoglobin. Poor absorption and utilization of iron and excessive loss through vomiting or diarrhea are given by Poncher (267) as important complicating conditions, as is loss in blood volume through clamping of the cord before pulsation has ceased. (See fig. 28.) Limitation of the diet to milk, which contains little iron, may also be a factor.

Diagnosis

Clinical signs

As in the early anemia, the most characteristic clinical sign of irondeficiency anemia, according to Diamond (83, p. 865), is pallor of the skin and mucous membranes "frequently associated with anorexia, a functional achlorhydria, irritability, fatigue, and weakness. In longstanding cases there may be definite retardation in skeletal and muscular development. The heart rate is usually increased, and there may be cardiac enlargement with easily audible murmurs. . . . The spleen and liver are often slightly enlarged."

Laboratory diagnosis

According to Diamond, the hemoglobin count is low (10-4 mg., or 65-25 percent); the erythrocyte count, 4,000,000 to 5,000,000 per cu. mm. at first, tends to fall to 3,000,000 or less; microcytes containing little hemoglobin pigment predominate in the peripheral blood; the number of leucocytes is usually reduced but not the number of plate-lets. Smith (321) believes the most reliable sign of iron-deficiency anemia is the reduction in the hematocrit measurement, which is much more extreme than the reduction in the number of cells. The reticulocyte count should be taken because, as Smith says, it "reflects the state of activity of the bone marrow" and thus serves as a guide both in diagnosing the disease and in gauging the response to treatment.
Differential diagnosis

A careful history, physical examination, laboratory data, and roentgenographic study are regarded by Diamond (83) as essential for finding all possible causes and distinguishing iron-deficiency anemia from anemia caused by congenital malformations, acute or chronic infections, and other conditions. Iron-deficiency anemia, moreover, may be masked, he says, by symptoms of vitamin-deficiency diseases such as rickets and scurvy, with which it is frequently associated. Smith (321) observes that since the onset is insidious, noting the effect on the hemoglobin of the administration of iron is helpful in preliminary differential diagnosis.

Treatment

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The type and amount of treatment required by premature infants with iron-deficiency anemia vary with the severity of the symptoms and the associated conditions. Administration of iron is quickly effective against iron-deficiency anemia alone, but if infection is present iron is ineffective until the infection is controlled. The forms of iron commonly recommended are ferrous sulfate or ferrous gluconate and ferric ammonium citrate. Diamond says that when ferrous sulfate is used it should be given by mouth between feedings, as the phosphorus in the milk tends to prevent absorption. According to Poncher (267), dosage is subject to wide variation, but he recommends for infants (without mention of premature infants) 4 to 6 grains (0.26-0.39 gm.) of ferrous sulfate daily for the treatment of iron-deficiency anemia. Josephs recommends for premature in-fants the use of ferric ammonium citrate (10-percent solution) in daily doses of 2 cc. per kg. of body weight. (Personal communication from H. W. Josephs, M. D., Johns Hopkins Hospital, Baltimore, Feb. 1948.)

Poncher (267), in a review of treatment of anemia in infancy and childhood, points out: "The controversy concerning the relative value of various preparations of iron can be settled practically by stating that since larger doses of ferric salts are necessary than with the ferrous form and since large doses of iron are irritating to the gastrointestinal tract, the practical expedient is to use the preparation less apt to upset the infant or child, other factors being equal. Organic preparations of iron in the ferrous form have been preferred by some for this reason. Ferrous gluconate is an example and is an acceptable preparation. The parenteral use of iron is seldom necessary and is a painful procedure. The amount of iron present in the preparation is no index of its efficacy. It is the amount of iron absorbed and utilized, not the actual iron present, that controls hemoglobin regeneration.

"The initial dose of iron should be small, and optimal doses should be approached gradually. The effectiveness of the preparation or adequacy of the dose of iron may be checked by the reticulocyte count just as one does with liver extract or folic acid in pernicious anemia. Within about 3 days after iron therapy is begun the reticulocytes begin to rise and reach a peak in 7 to 10 days. The level of hemoglobin and the peak of reticulocytosis is usually in an inverse ratio. The lower the initial hemoglobin value the higher the reticulocyte response which one will obtain with adequate iron medication, and this holds

true with the daily increase of hemoglobin in response to treatment. The rate of increase of hemoglobin in response to iron therapy definitely slows as normal values are approached."

In severe cases of anemia or in the presence of complications transfusions of typed and cross-matched blood may be necessary. Small amounts of blood (about 20 cc. per kg.) repeated two or three times are usually recommended. Transfusions are especially necessary when the anemia is associated with infection, which interferes with the efficacy of iron.

Prevention

To prevent iron-deficiency anemia in premature infants administration of iron (2-4 gr., or 0.13-0.26 gm., of ferrous sulfate or 0.2 cc. per kg. of body weight of ferric ammonium citrate in 10 percent solution), beginning from the sixth to the twelfth week of life, is advised. For infants of especially low birth weight the prophylactic iron might well be begun at 6 weeks. The milk feedings should be supplemented with iron-containing foods at as early an age as possible.

(For discussion of hemolytic anemia see Erythroblastosis Fetalis, p. 284.)

Summary

ERYTHROBLASTOSIS FETALIS

Erythroblastosis fetalis, or hemolytic anemia of newborn infants, is characterized by excessive destruction of erythrocytes and by extensive compensatory overdevelopment of erythropoietic tissue chiefly in bone marrow, liver, and spleen. Numerous nucleated red cells are found in the peripheral blood while anemia develops as a result of hemolysis.

Before the cause of this condition was known it was recognized that congenital hemolytic anemia, hydrops fetalis, and icterus gravis neonatorum were different manifestations of the disease erythroblastosis. Later it was shown that this syndrome, known as erythroblastosis, is the result of a specific blood reaction due to incompatibility of fetal and maternal blood in the Rh factor; that is, the mother is Rh negative and the infant Rh positive through inheritance from the father.

The mechanism is the immunization of the Rh-negative mother by the Rh-positive cells of the fetus or by a previous transfusion with Rh-positive blood; the production by the mother of an anti-Rh agglutinin; the passage of this soluble substance into the circulation of the fetus; the destruction of the erythrocytes of the fetus after specific reaction with anti-Rh agglutinin.

It is stated that 85 percent of the white population and 95 to 98 percent of the Negro population are Rh positive. Although it is estimated that in about 13 percent of all marriages the man is Rh positive and the woman Rh negative, the incidence of erythroblastosis is relatively low—0.1 to 0.66 percent of births.

The low incidence of erythroblastosis is due to a number of factors, among them the inheritance of the father—that is, whether he is heterozygous or homozygous in relation to the Rh factor; the number of pregnancies of the mother with an Rh-positive fetus; the permeaWith succeeding pregnancies the danger of sensitization of the mother increases. If she has had previous transfusions with Rhpositive blood, sensitization has been begun, and the first pregnancy with an Rh-positive fetus will frequently result in fetal erythroblastosis.

The clinical diagnosis of erythroblastosis is based on the following signs: jaundice within 24 to 48 hours after birth; anemia present at birth or within 3 or 4 days after birth; edema noted at birth or within the first 24 hours. The hydropic infant is usually stillborn or dies in the early neonatal period. Severe jaundice (icterus gravis) has a serious prognosis also, since the central nervous system may be involved (kernicterus). When anemia is the predominant symptom hemorrhages in the skin or mucous membranes may occur. Jaundice may be present also. The liver and spleen are usually enlarged.

The laboratory diagnosis depends on the demonstration in blood smears, made in the first 2 days, of large numbers of nucleated red blood cells—10,000 to 100,000 per cu. mm. As the anemia progresses the number of nucleated red cells decreases, but a persistent macrocytosis is an important diagnostic sign.

The final diagnosis rests on the determination of the Rh blood type in the mother (Rh negative); in the father (Rh positive); and in the infant (Rh positive). Tests for other blood groups (Hr, M, N, and P) may be necessary since cases of erythroblastosis have occurred as a result of incompatibility in these groups.

Erythroblastosis must be differentiated from a number of other conditions in newborn infants that cause similar symptoms, such as syphilis, congenital malformations of the liver and bile ducts, and hemorrhagic disease.

Treatment of erythroblastosis varies with the severity of the condition. Infants with mild symptoms may recover spontaneously. For those with more severe symptoms the specific treatment is repeated transfusion with Rh-negative blood (not from the mother), properly typed and matched for the international blood groups (A, B, AB, and O). In cases in which the mother has a history of having had one or more erythroblastotic infants transfusion for the infant immediately after birth is probably indicated. In some cases in which severe symptoms are present at or shortly after birth, "replacement" transfusion has been found effective. General supportive treatment for combating dehydration and maintaining body temperature and nutrition are indicated. The sensitized Rh-negative mother should not be allowed to nurse her infant because her milk may contain Rh agglutinins.

Although there is no way known at present to desensitize a sensitized Rh-negative woman there are a number of ways of preventing erythroblastosis. One of them is to take steps to decrease the isoimmunization of the female population that results from transfusion of Rh-negative females with Rh-positive blood. The Rh-negative mother should be advised to have no further pregnancy until at least a year after all residual agglutinins have disappeared from her blood. In addition, it has been suggested, although the value of the procedure has not been exactly determined, that pregnancy be terminated before term to shorten the period of intrauterine hemolysis, provided periodic tests of the mother's blood show that the Rh antibodies are increasing. Artificial insemination and "some form of birth control" have both been suggested as ways of dealing with this problem in an Rh-negative woman who has had children with erythroblastosis.

HEMORRHAGIC DISEASE

Newborn infants have a tendency to spontaneous hemorrhage in the early neonatal period which is said to occur more frequently in premature than in full-term infants.

Variations in the reported incidence of hemorrhagic disease are largely due to lack of adherence to the definition of this condition, which typically is hemorrhage accompanied by a hypoprothrombinemia more extreme than that which is physiologic among all infants during the first week of life. Vitamin-K deficiency is considered to be the cause of the hypoprothrombinemia; but as hypoprothrombinemia may occur without hemorrhage and hemorrhage without hypoprothrombinemia, some authorities suggest that a second and as yet unexplained factor may also play a part.

The disease is rare, the highest incidence among the reports cited being 0.8 percent.

Clinical manifestations are external or internal hemorrhages, or both, in various parts of the body. The diagnosis rests upon exclusion of trauma, infection, and jaundice as the cause of hemorrhage and the laboratory finding of a prolonged prothrombin time. Bleeding is said to occur usually when prothrombin activity is less than 20 percent of normal.

Treatment consists in administration of vitamin K intramuscularly or intravenously and repetition of the dose if indicated. Some authorities advise, in addition, immediate transfusion of compatible fresh whole blood.

• Hypoprothrombinemia can be prevented by administration of vitamin K to the pregnant woman during labor and to the premature infant at birth. Opinions differ as to the effectiveness of prophylactic administration of vitamin K in preventing hemorrhagic disease and in lowering neonatal mortality. To be on the safe side, however, it seems wise to give vitamin K to pregnant women and to all premature infants.

ANEMIA

Premature infants tend to develop anemia, particularly the socalled physiologic anemia of the early neonatal period and an irondeficiency anemia that begins in the second or third month of life.

The **neonatal anemia**, which occurs in full-term infants also, tends, in premature infants, to be more pronounced and to persist longer than in full-term infants. It is more severe the more premature the infant. The condition may be associated with changes in the oxygen saturation of the blood which take place at birth, with blood dilution resulting from rapid growth, or with too early clamping of the cord.

The diagnosis is made from clinical signs, such as pallor of the skin and mucous membranes, which usually is not apparent in the early period, and by examination of the blood, which shows a downward trend in the hemoglobin concentration and the erythrocyte count in the early weeks of life. When the hemoglobin concentration and red-blood-cell count reach extremely low levels or fail to return to normal within 2 or 3 months the condition must be considered evidence of some pathologic process, such as an infection, and not the result of prematurity per se.

Treatment is usually not required unless the anemia is very severe. In these cases repeated small transfusions of properly typed and crossmatched blood are recommended.

An *iron-deficiency anemia*, common in full-term infants in the second half-year, is likely to develop considerably earlier and to be more severe in premature infants. The underlying causes of this type of anemia in premature infants are the immaturity of the hematopoietic system, rapid growth in the presence of relatively low stores of iron, limitation of the diet to milk (low in iron content), and a tendency to infection and to diarrhea and vomiting.

The chief clinical signs are pallor of the skin and mucous membranes, anorexia, and slight enlargement of the liver and spleen. Examination of the blood shows a low level of hemoglobin (10-4 mg., or 65-25 percent); a falling erythrocyte count (from 4 or 5 million to 3 million or less); a low reticulocyte count; and reduction in the hematocrit measurement. In this type of anemia a careful history, physical examination, and laboratory studies are important to determine the underlying cause of the anemia.

Treatment is required for the condition responsible for the anemia and for the iron deficiency. Iron is usually given to premature infants in the form of ferric ammonium citrate or ferrous sulfate.

Measures for prevention of iron-deficiency anemia are administration of iron beginning at the sixth to the twelfth week of life and addition to the diet as early as possible of iron-containing foods.

METABOLIC DISTURBANCES

Acidosis

Premature infants have been said to have a tendency to develop acidosis in the early neonatal period. This "spontaneous" acidosis is attributed to defective renal function, and to peculiarities in water and acid-base metabolism. It has been found that premature infants are apparently unable to excrete an excess of acid and to metabolize acids as do full-term infants and adults. This is indicated, according to Gordon (118, p. 332), by the finding in a group of premature infants with spontaneous acidosis "of a plasma content of organic acids two to three times that of the full-term infant and the adult. It was found also that premature infants excreted two to five times the normal adult amount of organic acid per kilogram of body weight per day. No ketone bodies were present in the urine. Lactic-acid excretion in the urine of premature infants has been found to be more than 60 percent higher than that of full-term infants, while the plasma of premature infants may have as much as 7 to 15 millimoles of organic acids per liter as compared with only 2 to 3 millimoles for adults."

Smith (322) has supported this view but in a recent publication (323) he points out that there is some evidence that premature as well as full-term infants have considerable ability to maintain acidbase equilibrium. Data have accumulated to show that premature infants do not necessarily pass through an acidotic phase after birth. The pH is lowered very slightly but is stabilized to adult levels by the end of the first day; the chloride ion in the blood is increased and the bicarbonate ion is decreased but in spite of these changes "renal and respiratory control appear to cover the exigencies of the situation remarkably well and the deviations are comparatively minor ones."

Premature infants may also develop acidosis after the neonatal period as a result of abnormal conditions causing increased production of acid metabolites in the body; ingestion of acids or acid-producing salts or failure of the kidneys to excrete anions as rapidly as they accumulated in the blood and excessive loss of mineral cations (Na and K) and bicarbonate in diarrhea. As Guest (133) points out, "In conditions such as these, dehydration and acidosis are closely interdependent, each aggravating the other."

DEFINITION

Acidosis is defined by Peters and Van Slyke (258, p. 871) as an abnormal condition caused by the accumulation in the body of an excess of acids or the loss from the body of alkahi. They go on to say that "the more common cause is accumulation of acid, that is, a state in which acids are formed or absorbed more rapidly than they are destroyed or eliminated. The process may be considered to have

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produced a state of acidosis when it has caused either the bicarbonate of the blood to fall or the hydrogen ion concentration to rise above the normal limits."

Abnormal acid-base conditions of the blood may be metabolic or respiratory in type. In metabolic acidosis the primary disturbance is in the balance between alkali and acids other than carbonic acid; in respiratory acidosis the primary disturbance affects the carbon dioxide (CO_2) tension or carbonic acid (H_2CO_3) content of the blood. Peters and Van Slyke (p. 945) employ the term "alkali deficit" to denote metabolic acidosis and the term "carbon dioxide excess" to denote respiratory acidosis. The terms "compensated" and "uncompensated" acidosis are commonly used, according to Guest (133), "to denote whether or not the pH of the blood is maintained within normal limits by the buffer systems and physiologic mechanisms that govern the concentration of different components of the electrolyte system."

DIAGNOSIS

Clinical signs

Anderson (23, p. 236) describes clinical evidences of acidosis in mature infants as "sluggishness or marked restlessness, failure to suck well, failure to gain or loss of weight, an appearance of anxiety or fatigue, or dehydration, with or without some degree of hyperpnea." It is obvious that these signs with the exception of hyperpnea are very general in nature and that, although acidosis may be suspected, the diagnosis can be established only by laboratory means.

Laboratory diagnosis

In acidosis in infants the CO₂ content of the blood plasma is reduced with or without a reduction in the pH. The organic-acid content of the plasma may be high and varies inversely with the CO_2 content of the blood; the total base, chlorides and total blood protein are usually within normal limits.

Normal values for the chemical constituents of the blood of children and of infants from several sources are shown in table 58. The values for plasma carbon dioxide and for the pH in metabolic and respiratory acidosis in children, as given by Guest (133), are shown in table 59.

TABLE 58	Normal values reported	l for certain	chemical	blood	findings	in	infants
	and children				-		

2	Milliequivalents per liter of plasma or serum				CO ₂ (vol.		
Sources of data	Total base	Sodi- um	Chloride	Bicarbon- ate (HCO3)	percent)	рн	
Values for children: Guest ¹ Mitchell-Nelson ³ Values for infants: Hoag and Kiser ⁴ Smith ⁴	155 150-160 152. 4	137-146 144. 0	103 95–108 106. 2±2. 65 106. 9	27 19–30 23. 4±1. 57 22. 1	50-65 3 45-70 54. 4±3. 31 52. 1	7. 35–7. 45 7. 30–7. 45 7. 528±0. 047 7. 27–7. 47	

¹ (133). Determinations made in plasma.
 ² (248). Determinations made in serum -figure for pH is for serum or plasma.
 ³ Equivalent to 20. 3 to 31.5 millimoles per liter.

(322). Not stated if determinations were made in serum or plasma.

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If only one chemical test for acidosis can be made, it should be the determination of the CO_2 content of the blood.

TABLE 59	H ₂ CO ₃ -BHCO ₃	Buffering	of	Blood Plasma	in	Different	States	of
	Acidosis (Guest)	-						

	BHCO ₃ H ₃ CO ₃ CO ₃ ten- sion			рĦ	
Metabolia asidasia:	Meq. per l.	Vol. per 100 cc.	Meq. per l.	Mm. Hg.	
(b) Compensated	15 15	33 33	1.35 0.75	45 25	7. 14 7. 4
(a) Uncompensated CO ₂ excess	27 45	60 100	2. 28 2. 28	76 76	7. 16 7. 4

A report of spontaneous acidosis in 26 newborn premature infants weighing between 1,275 and 2,470 gm. has been made by McBryde and Branning (222). The abnormal signs were sluggish nursing, failure to gain weight, and some difficulty in breathing, interpreted as hyperpnea. Hyperpnea was present in 21 of the 26 infants. The CO_2 combining power of the blood plasma of all of the infants was found to be low. None of the infants had vomiting or diarrhea and no cause for the acidosis was determined.

TREATMENT

The treatment of acidosis, Butler and Talbot (57) point out, is directed toward the repair of losses of water and electrolyte incident to dehydration and toward provision of daily maintenance needs.

No one method of treatment of acidosis fits every case. The treatment must be individualized for each infant in relation to the severity of the symptoms of acidosis and to its underlying cause. (See p. 263.)

In mild cases of acidosis the treatment is relatively simple. In the cases of acidosis in newborn premature infants reported by McBryde and Branning the administration of one-sixth-molar sodium-lactate solution resulted in the rapid disappearance of symptoms. In more severe cases great skill and judgment are required to provide suitable therapy. It is being stressed more and more that for premature infants it is desirable to keep the salt intake at a minimum by the use of hypotonic solutions. Butler (56) gives parenteral therapy as follows: ". . we start by giving half-isotonic solution of sodium chloride or a mixture of two parts of half-isotonic solution of sodium chloride and 1 part of one-twelfth-molar sodium lactate in 5-percent dextrose solution, in a dosage of 10 to 15 cc. per kg. of body weight." In addition, he uses a multiple electrolyte solution. (For composition see (65).

The repair of intracellular loss in dehydration is outlined by Butler and Talbot (57) as follows:

- 1. Transfusions of whole blood or plasma to sustain red-cell and plasma volumes and plasma protein concentration.
- 2. Provision of amino acids.
- 3. Starting of oral feedings as soon as possible, including dextrose and vitamins, particularly C and B complex.

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They point out the possible need of providing 10 to 15 percent dextrose in maintenance parenteral therapy when relatively moderate total volumes of solution are infused at a slow rate, but when a larger volume of repair solution is being rapidly infused in the initial therapy of severe dehydration, a concentration of 5 percent dextrose in the parenteral fluid appears to provide a total amount adequate to meet caloric requirements.

Dodd and Rapoport (87) in discussing the treatment of acidosis in connection with intravenous alimentation of infants with diarrhea state: "To premature and very young infants in whom high chloride values in the plasma were observed, probably owing to small loss of chloride with diarrheal stools, less salt-containing fluid was given for correction of dehydration and maintenance. Initially, in order to avoid embarrassment of the circulation of severely dehydrated patients by the use of hypertonic solutions, 50 to 100 cc. of physiological saline were administered rapidly. The acidosis was then corrected by 3.7 percent sodium bicarbonate solution. In patients with mild acidosis, sodium lactate was used when correction was indicated. In most cases blood, plasma, casein hydrolysate, and hypertonic solutions of glucose or glucose in saline were administered by means of a slow intravenous drip only when dehydration was largely overcome. In cases of severe circulatory collapse, extreme malnutrition, or anemia, blood and plasma were occasionally given in the first 24 hours. The frequent occurrence of hypocalcemia with attendant symptoms during the postacidotic phase ... led to the use of oral or parenteral calcium therapy." When casein hydrolysate is used "a closed system of fluid administration and rigid precautions against contamination were found necessary in the use of this solution, as it is an excellent culture medium for bacteria." (See section on treatment of diarrhea, p. 266.)

Rapoport and his coworkers (287, pp. 430, 441) have found that in infants, particularly premature infants, with diarrhea and acidosis, correction of the acidosis by alkalinizing agents may accentuate the tendency to a "postacidotic disturbance." The clinical picture is characterized by lethargy or irritability, convulsions, respiratory embarrassment, derangements of cardiac function, intracranial and gastrointestinal hemorrhages, and generalized edema. Low levels of calcium, potassium, phosphorus, and phosphatase are found. Calcium salts have been of benefit, he says, in preventing or curing the postacidotic phase of diarrhea. A case report is given of this condition in a 2-month-old premature twin. "When the alkalotic condition of the infant was realized, calcium chloride therapy was instituted in a dosage of 3 gm. daily for a period of 2 days. The serum calcium, 8.4 mg. on the first examination, rose to 11.7 mg. per 100 cc. after treatment, and recovery took place."

Gordon has expressed the opinion that although the use of bicarbonate brings about rapid correction of acidosis this is not as desirable as more gradual correction with one-sixth molar lactate solution. (Personal communication from Harry H. Gordon, M. D., Colorado General Hospital, Denver.)

PREVENTION

Smith (322, pp. 256-257) calls attention to the need for regard for the physiologic peculiarities of newborn infants. "The physician

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should note that dehydration is not to be overlooked as completely normal and harmless, nor on the other hand to be overcorrected by the too frequent or lavish use of salt solutions hypodermically. Edema is easily produced by this means, and, indeed, it not uncommonly occurs spontaneously during the newborn period. If the kidneys are already faced with some difficulties in the way of excreting salt, to add any excess of electrolytes is obviously an error. Guidance will be gained from inspection of the temperature and weight chart, and particularly of the baby itself, for a satisfactory weight chart may actually mean an edematous infant. Albuminuria and mild azotemia cannot necessarily be taken as signs of abnormality. Should the infant still be losing weight after the fourth day, particularly if the temperature is above normal, and should inspection show evident dehydration, from 10 to 15 cc. of normal salt solution per pound may be given hypodermically. Larger amounts will of course be needed if abnormal fluid losses, such as from diarrhea or vomiting, are occurring. Under such conditions, especially in premature infants, measurement of blood bicarbonate (or CO_2 combining power) usually shows an unexpectedly marked shift toward an acidosis which will require the prompt use of lactate or bicarbonate and glucose solutions for its correction."

Hypoglycemia

A low blood-sugar level is commonly found in normal newborn infants. Premature infants apparently tend to have a still lower level.

Though many studies have attempted to establish a norm for bloodsugar content at birth, the results, because of "the use of conflicting methods for blood collection and measurement and from a characteristically wide range of glucose concentration," show such wide variations that Smith (322, p. 201) believes a "normal" figure has little value. He adds, however, that "independent investigations have shown essentially similar trends," such as a marked decline immediately after birth, great individual variation, and a rising tendency about the third day.

The figures obtained by a modified Folin-Malmros technique in a study of the blood-sugar content of newborn infants by Ketteringham and Austin (181, p. 328) (table 60) illustrate these points. Hartmann (138, p. 21) gives the "normal fasting level" of blood

Hartmann (138, p. 21) gives the "normal fasting level" of blood sugar as varying between 60 and 100 mg. per 100 cc. by his method of measurement, except in very young infants. "Although the symptoms of hypoglycemia are not necessarily very closely correlated with the exact level of blood sugar," he considers that there is mild hypoglycemia if the level is 40 to 60 mg., moderate hypoglycemia if the level is 20 to 40 mg., and extreme hypoglycemia if the level is 0 to 20 mg. These figures relate to what Hartmann calls "true" (yeast-fermentable) dextrose.

CAUSE

According to Rapoport (285), hypoglycemia may be due to disturbance in the rate at which glucose enters the blood or to an increased rate of removal of glucose from the blood by the body tissues (hyperinsulinism). In the former category he puts "starvation hypo-

Metabolic Disturbances

glycemia," or an inadequate supply of glucose for 24 to 48 hours, such as may occur during diarrhea, vomiting, and other conditions; renat glycosuria; pituitary or adrenal cortical insufficiency; and liver disease, causing disturbance in carbohydrate metabolism.

	Number	Mg. per 100 cc.		
Age	of infants	Mean	Range	
At birth First day Second day	47 45 41 42	104 68 70 76	47-102 52-103 57-110	

TABLE 60 Blood-sugar levels of newborn infants (Ketteringham and Austin)

In regard to premature infants Smith (322, p. 202) states: "While no relationship has been demonstrated between blood sugar and birth weight in full-term infants, the few studies on the blood of premature infants usually have shown glucose concentrations still lower than those found after full-term birth. In a minority of observations this was not the case. Haass (135) concluded that the lowering of blood sugar in prematures was related more to the temperature of the infant than to its weight or gestational maturity; indeed his protocols show that quite regularly the infants became much less hypoglycemic as their temperatures were brought up, and this often occurred within an interval so short that little 'development' of regulating centers could possibly have taken place. Van Creveld (363) also found low blood-sugar values in premature infants. While he unfortunately does not mention the body temperature of his subjects he gives the impression that the subsequent rise in these figures was so gradual as to make changes in temperature of no significance in their explanation . . . It was his general conclusion that this peculiarity of premature infants was not due specifically to hyperinsulinism, starvation, deficiency of liver glycogen, or any specific factor other than general functional immaturity."

When the infant of a diabetic mother is found to have hypoglycemia it is often assumed that abnormal symptoms in the hypoglycemic infant are related to the maternal diabetes. Miller and Ross (234) have pointed out that, although this may be the case, the infant's abnormal symptoms may be, and in their experience often are, due to conditions other than maternal diabetes per se.

Miller and Ross (234, p. 479) reported (table 61) the blood-sugar levels during the first 48 hours of life in normal full-term and pre-

TABLE 61	Blood-sugar levels of normal full-term and premature infant	:8
	and of infants of diabetic mothers (Miller and Ross)	

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	Full-term infants	Premature infants	Infants of diabetic mothers
Number of infants.	Gm. per 100cc.	Gm. per 100cc.	Gm. per 100cc.
Number of determinations.	17	20	6
Blood sugar:	28	40	17
A verage.	0.0499	0.0318	0. 0297
Standard deviation from the mean	±0.0125	±0.0124	±0. 0120

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mature infants that they examined, compared with those of newborn infants of diabetic mothers.

The authors conclude that (1) the average blood-sugar concentration in infants born of diabetic mothers is significantly lower than in normal full-term infants; (2) some of the blood-sugar concentrations in the normal full-term infants are as low as some included in the group of infants of diabetic mothers; (3) the blood-sugar concentrations in normal premature infants average practically the same as those of infants whose mothers have diabetes.

Miller and Ross (p. 479) point out that the blood-sugar concentrations reported by them "are in agreement with those of other investigators with the exception that the blood-sugar concentrations in our study are generally lower than those usually reported." This is probably dependent, they state, on the method they used. They made duplicate analyses by the Folin-Malmros method but used their own method in the first instance.

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DIAGNOSIS

In very young infants, Rapoport (285) says, it may be difficult to recognize or evaluate the symptoms of hypoglycemia, which show great variation and are not always related in severity to the bloodsugar level. Among the symptoms that he lists are fatigue, flushing, sweating, vomiting, subnormal temperatures, tachycardia and extra systoles, tremors, paralysis, syncope, and convulsions. The diagnosis, if suspected from clinical symptoms, however, should be confirmed, he says, by glucose-, insulin-, and epinephrine-tolerance tests, the results of which, however, "should be interpreted with caution (p. 1175)."

Hartmann (138) reports that in "roughly one-half of the infants born of diabetic mothers which we have been able to study, severe hypoglycemia with symptoms occurred during the first day or two of life." Symptoms varied between mild ones (restlessness and cyanosis) and more severe ones (unconsciousness and convulsions). The severity of the symptoms was not always related to the blood-sugar levels. Hartmann classifies these cases (p. 27) as "temporary true hyperinsulinism due to hyperactivity of the islands of Langerhans, which was physiologic and induced by the occurrence of hypoglycemia."

Hartmann and Jaudon (139, p. 35), in a comprehensive study of 286 cases of hypoglycemia in infants and children occurring at the St. Louis Children's Hospital over a period of 15 years, concluded that (1) hypoglycemia occurs quite regularly during the first 4 or 5 days of life in normal newborn infants and seems to be due to "an imperfectly developed regulatory mechanism which creates a state of relative hyperinsulinism"; (2) a similar period of hypoglycemia occurs in infants of diabetic mothers.

Miller and Ross (234, p. 473) point out: "The belief is widely held that the hypoglycemia of newborn infants whose mothers have diabetes mellitus is the cause of the cyanosis, muscular twitchings, convulsions, and occasionally the death of the infant." They report their observations of 6 infants of diabetic mothers. All the infants had hypoglycemia; 3 had abnormal clinical findings that had a physical basis not associated with the hypoglycemia, and in these 3 cases there was no clinical improvement with administration of glucose. A premature infant that, in the early period after birth, develops symptoms such as twitchings, convulsions, or evidences of collapse may be suffering from hypoglycemia that is the result of a prediabetic or diabetic condition in the mother. There are other conditions that may account for the symptoms, such as cardiac hypertrophy with failure, tetany, erythroblastosis, atelectasis, and intracranial or adrenal hemorrhage. Since in newborn infants, especially premature infants, the blood-sugar concentration tends to be low at birth and in the first few days following birth, blood-sugar determinations, unless the level is extremely low, are of little use in the differential diagnosis.

TREATMENT

If symptoms are pronounced and hypoglycemia is diagnosed the treatment called for, according to Rapoport (285), is administration of glucose and of 0.03 cc., or $\frac{1}{2}$ minim, of a 1:1000 solution of epinephrine per kg. of body weight. With young infants the former is usually and the latter is always given parenterally.

According to Hartmann and Jaudon (139, p. 35), the hypoglycemia that develops in infants of diabetic mothers "may be prevented or controlled quite effectually by the combined use of epinephrine and dextrose injection as emergency measures, and the prophylactic starting of complemental milk and carbohydrate feedings immediately after birth. The most careful observation of such infants for the first 4 or 5 days of life (with special nurses, if possible) seems almost necessary." The infant that is in an acute state of collapse may be suffering from insulin shock and should be treated accordingly.

It is very important, however, as Miller and Ross (234) have pointed out, to be certain that symptoms in the infant of a diabetic mother are not the result of some condition other than hypoglycemia and, if they are, to treat the condition that is the true cause of the disturbance.

Hypoproteinemia

Hypoproteinemia is a condition in which the level of protein in the blood serum is lower than the normal level, either in albumin or in globulin, or in both. The amount of protein in an arbitrary amount of serum or plasma is the measure commonly used, but Metcoff and Stare (231) believe that total blood volume should also be taken into consideration. They say: "Since the volume of circulating plasma is subject to considerable change in relation to growth, health, and acute and chronic disease, it is evident that significant changes in quantities of circulating plasma protein may be masked if the protein concentration is measured without regard for expanding or contracting blood volume."

Premature infants are handicapped in the neonatal period by a relatively low level of serum protein, which appears to be due largely to globulin deficiency. The condition may be in part the result of hepatic immaturity, although other factors may be involved. In the liver many fractions of the serum proteins are formed, among them globulin and albumin. Rapoport (283, p. 662) says that the liver also appears to serve as a storage depot for protein and that the storage is influenced by the adequacy of protein in the diet. Gordon and his coworkers (122) have shown by balance studies that the premature

infant's ability to digest and absorb protein is at least as great as that of the full-term infant.

The premature infant, because of rapid growth, has a higher requirement for protein than the full-term infant. In addition, the tendency for premature infants to acquire infections in the neonatal period appears to be the result of the inadequate antibody production which is characteristic of all young infants combined with the lack of passive immunity from the mother which is the result of premature birth. The inadequacy of antibody production, according to Smith (322, p. 293), "may well be related to the characteristically low concentration of serum (and cellular) globulins in young infants."

Comparatively few studies have been made of the serum-protein levels in premature infants, but a number have been made of the levels in full-term infants. The studies show considerable variation in average figures for total protein and for globulin and albumin levels, and a wide range in the levels of individual infants. The variations are related to the chemical methods used in analyses; to the ages of the infants at the time the levels were determined; to their protein intake; and to the presence of pathologic conditions such as vomiting or diarrhea.

Metcoff and Stare (231) give figures from Rapoport, Rubin and Chaffee (286) for average plasma-protein, globulin, and albumin levels for premature and full-term infants and from Trevorrow and associates (357) for these levels in full-term infants at birth. (Table 62.) The figures given for plasma albumin are slightly lower in premature infants than in full-term infants, but the figures for plasma globulin are markedly lower in premature infants.

TABLE 62	Normal plasma-protein concentrations ¹ (quoted by Metcoff and Stare
	from figures given in two previous studies)

Infants	Total	Albumin	Globulin
	protein (gm.	(gm. per	(gm. per
	per 100 cc.)	100 cc.)	100 cc.)
Full-term infants ^{2 3} Premature infants ² (aged 1 to 68 days)	$\begin{cases} 5.11\pm0.76 \\ to \\ 5.70\pm0.45 \\ 4.55\pm0.59 \end{cases}$	3. 76±0. 43 to 3. 79±0. 33 3. 55±0. 65	1. 34 ± 0.41 to 1. 66 ± 0.29 1. 01 ± 0.45

¹ Most of the reported total protein values are derived from micro-Kjeldahl analyses, and the albumin and globulin, from sodium-sulfate fractionation.

² (357). ³ (286).

McMurray, Roe, and Sweet have reported the plasma-protein values (total protein, albumin, and globulin) in the blood of 39 full-term and 39 premature infants, divided into six groups according to weight. The method used was a modification of the Greenberg method with use of the Kingsley procedure for separating globulin from albumin. (Manuscript submitted for publication.)

(Manuscript submitted for publication.) The mean plasma-protein value for all premature infants during the first week of life was found to be 5.6 gm. per 100 cc. of plasma; the albumin, 4.3 gm.; and the globulin 1.6 gm. For full-term infants in the first week the mean values were 6.4, 4.8, and 1.75, respectively. The authors point out that these values are higher than those reported by Darrow and Cary (76). They are also higher than those reported by other investigators. The mean total plasma-protein values and

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the albumin values thus determined one to three times in the first week of life were significantly lower for premature infants than for fullterm infants. In these two values the full-term infants were just below and just above, respectively, the lower limits given for normal adult values (total protein, 6.5-8.2 gm. per 100 cc.; albumin, 4.5-6.5gm. per 100 cc.). The difference between the full-term and the premature infants in globulin values was not statistically significant. The globulin values showed a slight rise with increasing maturity (weight), but in all cases they were within the normal adult range (1.2-2.2 gm. per 100 cc.) as given by the authors.

Young and her coworkers (411), using the micro-Kjeldahl method, found the average plasma protein in 12 normal (nonedematous) premature infants aged 3 to 5 days to be 4.63 gm. per 100 cc.; in 6 edematous premature infants aged 2 to 7 days, 4.56 gm. per 100 cc.; and in 8 normal premature infants aged 8 to 18 days, 4.42 gm. per 100 The authors comment that though these figures are below normal cc. adult values (6 to 8 gm. per 100 cc.), they are not necessarily abnormal because plasma-protein values tend to be low during the first year of life. The fact that figures for the edematous infants were no lower than for the normal infants, together with other factors studied, led the authors to the conclusion that the susceptibility of premature infants to edema is due, not to low plasma protein, though that may be a contributory cause, but primarily to imperfect kidney function leading to water retention.

Young suggests that the higher levels found by McMurray and her coworkers, higher than those reported by others, may be due to the chemical method that they used. In addition, she suggests that variations in the protein intake in the diet at the different age periods and the high incidence of infection in the control group may have influenced the findings. (Personal communication from W. F. Young, M. B., Children's Hospital, Birmingham, England, June 16, 1947.)

In order to establish normal values with increasing age and weight McMurray and associates made serial plasma-protein determinations on a group of premature infants but found values so irregular and erratic that they decided to administer albumin intravenously in the effort to obtain more stable results and to determine, if possible, the effect on growth.

Sixteen normal healthy premature infants weighing at birth 3 lb. 8 oz. to 4 lb. 8 oz. were given repeated intravenous injections of 2 or 3 cc. per lb. of body weight of concentrated normal human serum albumin (25 gm. of albumin per 100 cc.) at intervals that varied from four times a week to once a week. The plasma-protein levels were studied serially in these infants, and also in 17 control cases—healthy premature infants receiving identical management, diet, and nursing care but no albumin. By the end of the third week, the caloric intake was gradually increased to a daily average of 60 calories per lb. of which 2.2 gm. per lb. was protein.

The infants who received albumin showed a steady, progressive rise in total protein and albumin values, and the range in the values was narrower and less variable than in the control group, accompanied by an unexplained decrease in globulin. The authors noted also that the treated infants made a more rapid gain in weight and suffered fewer and less severe illnesses than the control group.

The authors point out that the number of infants observed was too small to permit final conclusions, that there is no present knowledge as to the mode of action of the intravenous albumin, but that the results warrant further study of the use of human serum albumin in the care and treatment of premature infants.

Further studies of protein levels in the blood of groups of premature infants, made under comparable conditions, are needed to determine normal and abnormal values and to establish prophylactic and therapeutic means of dealing with the problems involved. In the meantime the fact that premature infants require and can utilize more protein than full-term infants makes it clinically important to see that they receive ample amounts of protein in their diet. (See Nutritional Requirements, p. 146.)

Summary

ACIDOSIS

Premature infants tend to develop acidosis in the early neonatal period, which is attributed to defective renal function and to peculiarities in water and acid-base metabolism. These infants may also develop acidosis after the neonatal period as a result of certain abnormal conditions, particularly diarrhea.

Acidosis is defined as an abnormal condition caused by the accumulation in the body of an excess of acids or the loss from the body of alkali. Abnormal acid-base conditions of the blood may be metabolic or respiratory in type. In the former condition the disturbance is in the balance between alkali and acids other than carbonic acid; in the latter the primary disturbance affects the carbon dioxide tension or carbonic acid content of the blood.

Clinical signs of acidosis are general—sluggishness or restlessness, failure to suck well, failure to gain or loss of weight, and dehydration. Hyperpnea may or may not be present.

The laboratory diagnosis is based on the finding of a reduced serum carbon dioxide content with or without a reduction in the pH.

Treatment is directed toward correction of the acidosis, repair of losses of water and electrolyte, and provision of daily maintenance needs.

The treatment must be individualized for each infant in relation to the severity of the acidosis and its underlying cause.

To the dehydrated acidotic infant one-sixth or one-seventh molar sodium lactate solution should be given intravenously or subcutaneously. There is some danger in attempting more rapid correction of acidosis with sodium bicarbonate solution. Transfusion with whole blood or plasma is useful to sustain red cell and plasma volumes and plasma protein concentration. Dextrose solution added to the parenteral fluid provides calories. In addition, amino acids may be given. Oral feedings should be begun as soon as possible, including dextrose and vitamins C and B complex.

In cases in which severe diarrhea is a cause of acidosis it is recommended that, in addition to the one-sixth molar sodium lactate solution parenteral normal saline alone or with the addition of 5 to 10 percent glucose solution; blood or plasma; and a 5 percent casein hydrolysate solution in 10 percent glucose be given. If casein hydrolysate is given a closed system of fluid administration must be used and rigid aseptic precautions taken.

Prevention of acidosis demands close regard for signs of dehydration and edema; alertness for evidences of a tendency to acidosis; and the use of proper solutions for correction of these conditions.

HYPOGLYCEMIA

Premature infants tend to have hypoglycemia in the early days after birth. Studies of normal blood-sugar levels for full-term infants show wide variations because of differences in methods used and the wide range in individual infants. There is apparently, however, a fall right after birth and a rising tendency about the third day. A level of 60 to 100 mg. per 100 cc., however, has been suggested as the norm except in very young infants, with any level below 60 mg. indicating some degree of hypoglycemia and a range of 0 to 20 mg. indicating an extreme form.

Hypoglycemia has been found to occur quite regularly in normal infants and in infants of diabetic mothers. The cause is given as disturbance in the rate at which glucose enters the blood or an increased rate of removal of glucose from the blood by the body tissues, due to a variety of conditions.

The blood-sugar levels of premature infants have been found to be lower than those of normal full-term infants and to be comparable to those found in infants of diabetic mothers.

In very young infants diagnosis is often difficult because of great variation in symptoms, which are not always related in severity to the blood-sugar level. Clinical symptoms need to be confirmed by glucose, insulin-, and epinephrine-tolerance tests, though these should be interpreted with caution.

When premature infants of diabetic mothers have such symptoms as restlessness, cyanosis, or convulsions, a low blood-sugar level may be but is not necessarily evidence that the symptoms are due to the maternal condition. They may be manifestations of cardiac hypertrophy, erythroblastosis, or some other abnormal condition.

If symptoms are pronounced and hypoglycemia is diagnosed epinephrine and glucose should be administered, the former always and the latter usually by the parenteral route with young infants. This treatment is especially likely to be needed by infants of diabetic mothers, whose condition in the first few days of life calls for careful observation and skilled nursing care and may require emergency treatment.

HYPOPROTEINEMIA

Premature infants are handicapped in the neonatal period by hypoproteinemia (low serum-protein level) which appears to be due largely to deficiency in the globulin fraction, although albumin is deficient also. Globulin is important in relation to antibody formation.

The demands of the premature infant for protein are greater than those of the full-term infant. Their ability to digest and absorb protein has been found at least as great as that of the full-term infant.

Studies of the serum-protein level in premature infants show in general lower levels than in full-term infants. There is, however, considerable variation in the average levels reported and a wide range in the levels of individual infants. The differences are related to a

number of factors, among them differences in chemical methods used, age of the infants, protein intake, and the presence of pathologic conditions, particularly those in which diarrhea or vomiting has occurred.

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. Average levels of serum protein for newborn premature infants and full-term infants that are frequently quoted are as follows:

	Total protein (gm. per 100 cc.)	Albumin (gm. per 100 cc.)	Globulin (gm. per 100 cc.)
Full-term infants	5. 11	3.76	1.34
Premature infants	4.55	3.55	1.01

One study of premature infants in which serial protein, albumin, and globulin determinations were made throughout the period of hospitalization showed wide ranges and erratic variations. Concentrated human serum albumin given intravenously resulted in an increase in the total-protein and albumin levels and a decrease in the globulin levels which did not occur in the control group. The treated infants showed a more rapid gain in weight and suffered fewer and less severe illnesses than the control infants. The findings are suggestive but not conclusive because of the small number of infants studied.

Pending further studies of protein levels in the blood of premature infants to establish norms and prophylactic and therapeutic procedures it is clinically important that these infants receive in their diet ample amounts of protein.

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NUTRITIONAL DISTURBANCES

Rickets

Rickets is defined by Eliot and Park (97, p. 1) as "a disturbance in the calcium and phosphorus metabolism which prevents the normal deposition of calcium salts in the growing parts of the skeleton." This disturbance arises when the supply of vitamin D is deficient because vitamin D promotes the absorption and utilization of calcium and phosphorus.

In premature infants, according to Eliot and Park (*p. 8*), rickets tends to develop earlier, to progress more rapidly, and to be more severe than in those born at term. In addition, it has been found more difficult to prevent rickets in premature infants.

CAUSE

The tendency for premature infants to develop rickets is due to inadequate antenatal storage of calcium; poor mineralization of the skeleton; rapidity of growth, which increases the calcium requirement; inefficient utilization of the calcium and phosphorus in the food; inefficient absorption of fat, which may affect the utilization of fat-soluble vitamin D; and deprivation of direct sunlight over a relatively long period. The high incidence of infection and of diarrhea in premature infants is also a factor in their tendency to develop rickets.

DIAGNOSIS

Clinical signs

Clinical signs of rickets in premature infants usually do not appear until the third or fourth month. They are particularly insidious in their onset. Craniotabes may be the first skeletal sign. Tetany may also be an early sign of rickets in premature infants. (For discussion of tetany see p. 330.) Eliot and Park (97, p. 80) point out that "the reason why the premature infant seems to be differently affected than the child born at term is to be explained as follows: The head of the premature infant grows rapidly. [The fact that these infants tend to lie on their backs makes continuous pressure on the back of the The clinical signs of the disease in the head, therefore, become head.] conspicuous. The arms and legs, on the other hand, are moved but little and conspicuous deformities do not develop. However, the rachitic process at necropsy is found to be as advanced in the extremities as in the head. Even in the X-ray film the ends of the long bones may exhibit few or doubtful signs of rickets when the microscope will reveal advanced development." If the infants are untreated or in-adequately treated, the disease progresses and the classical signs of rickets appear-enlargement of the costochrondral junctions, par-

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ticularly noticeable in the ribs and wrists, enlarged frontal bosses, delayed closure of the fontanel and sutures of the skull, and prominent belly.

Roentgenographic evidences

Evidences of 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 are pathognomonic. They must be differentiated chiefly from those of syphilis (see p. 242) and of scurvy.

The roentgenograms should be made of the lower ends of the radius and the ulna, in which rachitic changes show up more distinctly than those in other locations. The hand and arm must be supinated and held flat, and if blurring, which can lead to incorrect diagnosis, is to be avoided, all movement must be prevented.

The earliest roentgenographic rachitic changes may be seen in the cortex and in the periosteum of the bones. Changes at the cartilage-shaft junction usually appear later.

Eliot and Park (97, p. 69) distinguished between the atrophic type of rickets, in which bone destruction predominates over bone formation and there is no healing tendency, and the hypertrophic type, in which there is a healing tendency, though it is not sufficient to end the disease. The cortex of the bone may appear thin or be invisible in places—the atrophic type—or it may appear thickened—the hypertrophic type. In the latter type (p. 92) "thickening of the cortex is usually greater on one side. The marrow cavity may be eccentric and its width be greatly reduced. In this type periosteal encasements are usually visible. Several layers sometimes may be seen, appearing as fine lines parallel to the cortex."

Osteoporosis and coarseness of the finer structure of the shafts of the radius and ulna were the only roentgenographic evidences of rickets in a 2-month-old premature infant reported by Eliot and Park (p. 80). The diagnosis of rickets was established by the level of inorganic phosphorus in the blood—2.9 mg. per 100 cc. of serum.

Park points out the inadequacy of roentgenograms for the early diagnosis of rickets. The signs of the disease are usually not seen in the films until the disease has progressed to a very considerable extent. This is particularly true in premature infants because in them the ends of the bones are not deformed from stress and strain. (Personal communication from Edwards A. Park, M. D., Johns Hopkins Hospital, Baltimore.)

Malmberg (220) considers that "periosteal proliferation" along the diaphysis of the long bones is the earliest roentgenographic sign of rickets, often appearing 4 to 6 weeks before the epiphyseal changes. Seventy-two premature infants were given prophylactic antirachitic therapy of varying intensity begun as early as the second half of the first week of life; 26 received daily 2,700 international units of vitamin D_s and 3 received 5,400 units, 29 received 10,000 units, and 14 received 500,000 units of D_2 in two doses from the fourth to the seventh day of life. Forty-two untreated infants served as controls. Repeated roentgenograms were made of costochondral junctions, the bones of

the forearm and leg, and in some cases the bones of the upper arm and thigh of the infants given prophylactic antirachitic treatment and also of the untreated infants. Calcium and phosphorus levels in the blood of these infants were not reported.

Many of the infants, both treated and untreated, showed in roentgenograms a linear periosteal deposit of calcium of varying length along the diaphysis, most commonly on the tibia but in some cases on the fibula, radius, femur, and humerus. It was generally observed at 4 to 6 weeks of age. In some cases the deposit appeared as a fine line; in some, as a thicker line; and in some, in the form of layers. The incidence of periosteal proliferation was much greater among the infants who did not receive vitamin D.

Of the 42 infants in the control group, 24 eventually showed roentgenographic evidence of rickets; of these 24 infants, 15 had had earlier periosteal proliferation and 9 had not. Seven of the 24 infants with rickets weighed between 2,001 and 2,500 gm. at birth.

Of the 72 infants that received vitamin D, 15 eventually showed roentgenographic signs of rickets and in addition 1 infant had questionable rickets; these 16 infants all weighed less than 2,000 gm. at birth. All but 2 of the 15 infants that developed roentgenographic signs of rickets were in the group of 29 infants that received the smallest daily amounts of vitamin D. It was in this group also that occurred the only instances among the treated infants in which rickets developed after no periosteal proliferation had been found; 9 of the 19 infants in this group that showed no periosteal proliferation developed subsequent roentgenographic signs of rickets. Of the 29 infants receiving 10,000 international units of vitamin D, 14 showed periosteal proliferation and 2 of these (1 weighing only 1,000 gm.) developed subsequent signs of slight rickets. Eleven of the 14 infants receiving 500,000 units of vitamin D showed no periosteal proliferation; of the 3 who did, 1 developed questionable rickets. (See Nutrition, p. 162.)

Park points out that periosteal proliferation may be due to any one of three conditions, which cannot be differentiated by roentgenograms alone: (1) early rickets; (2) overproduction of cortical material to correct weakness; (3) rapid growth. (Personal communication from Edwards A. Park, M. D.)

Sydow (344) considers the earliest sign of rickets to be metaphyseal decalcification, which usually appears in the first month of life and is usually followed by the accepted roentgenographic signs of rickets. He found that when the decalcification occurred in the second half of the first month serum-phosphatase values might be a little higher than the average for the age group but other serum values were not appreciably altered. Transverse lines in the shaft the author considered not connected with rickets. Park, however, considers that transverse lines are a sign of interrupted growth which is common in rickets. (Personal communication from Edwards A. Park, M. D.)

Evidences of later rickets

Eliot and Park (97) list the roentgenographic evidences of rickets at the cartilage-shaft junction as cupping, spreading, spur formation, fringing, and stippling. They are the same in premature infants as in full-term infants and are described in detail, with explanation of the underlying pathology, in the monograph by these authors.

Figure 30 illustrates the roentgenographic diagnosis of rickets in a premature infant. Figure 30-1 shows a roentgenogram made when

the infant was 60 days old. There appears to be slight osteoporosis of the shafts of the radius and ulna, which is suggestive, but the diagnosis of rickets could not be made from this film. Figure 30-2, from a roentgenogram made when the infant was 75 days old, shows the earliest definite signs of rickets—spreading and fringing of the distal ends of both radius and ulna and slight cupping of the ulna. Figure 30-3, from a roentgenogram made when the infant was 83 days old, shows florid rickets—fringing and spreading of the distal end of the radius and of the ulna and cupping of the ulna. Figure 30-4, from a roentgenogram made when the infant was 106 days old, shows healing rickets. There is evidence of calcium deposition at the diaphyseal-epiphyseal junction of the distal end of both bones, as well as in the cortex. The periosteal shadow has become visible on the inner side of the shaft of the ulna and on both sides of the shaft of the radius.

These films illustrate the point made by Caffey (59, p. 691) that "the early metaphyseal changes offer great difficulty for conclusive evaluation; they are best interpreted in retrospect from serial films." Park also emphasizes the importance of serial films because many times in his experience a doubtful diagnosis of rickets from an early film has been confirmed by films taken after treatment had been given. (Personal communication from Edwards A. Park, M. D.)

Sydow (344) made serial roentgenographic examinations of the wrist, as well as determinations of the calcium, phosphorus, and phosphatase levels in the blood, of 118 premature infants weighing at birth 1,010 to 2,000 gm. He found (*pp. 78, 79*) that more than half of the roentgenograms of the premature infants over 1 month of age showed the evidences of rickets, active or healed, as interpreted by Eliot and Park; a very few roentgenograms of infants under 1 month of age showed such evidences of rickets. Among infants 31 to 180 days of age rickets was shown in all examinations of the lowest birthweight group (1,010-1,500 gm.), in two-thirds of those of the middle-weight group (1,510-1,750 gm.), and in two-fifths of those of the high-est-weight group (1,760-2,000 gm.). (See also p. 327.)

Laboratory diagnosis

Determination of the *calcium and phosphorus* levels in the blood serum is a more accurate method for early diagnosis of active rickets than are clinical and roentgenographic signs. The serum calcium and phosphorus levels vary considerably during the first week of life. (See Tetany, p. 330.) After this period the levels tend to become stabilized. The constant concentration of calcium in the serum of healthy infants is given by Eliot and Park (97, p. 37) as 9.5 to 11.0 mg. per 100 cc., whereas the inorganic-phosphorus concentration is much less constant and varies with age. Smith (322, p. 225) gives an average of 10.45 mg., with a range of 7.5 to 13.9 mg., for calcium and 5.93 mg., with a range of 3.5 to 7.6 mg., for inorganic phosphorus, based on specimens taken from the fourth to the seventh day of life.

Eliot and Park say (**p. 38**): "In infantile rickets, the serum calcium remains at approximately 10 to 11 mg. per 100 cc., but the inorganic phosphorus usually lies between 2 and 4 mg." In tetany it is the serum calcium that is reduced; the inorganic-phosphorus level is usually normal. In rickets accompanying tetany the serum calcium and



Figure 30.—Serial roentgenograms showing the development of rickets in a premature infant (courtesy John Caffey, M. D., Babies Hospital, New York City).

- 60 days, doubtful rickets.
 75 days, early rickets.
 83 days, florid rickets.
 106 days, healing rickets.



not the phosphorus may be reduced. (See Tetany, p. 330.) In premature infants suffering from rickets, however, both calcium and phosphorus may be reduced. Eliot and Park comment that in these infants "it is especially common to find the inorganic phosphorus greatly reduced and the calcium moderately so." They cite (as a rather extreme example) the case of a 6-week-old premature infant showing marked craniotabes, who had a calcium concentration of 6.0 and an inorganicphosphorus concentration of 3.4 mg. per 100 cc. They emphasize (*p.* **80**), however, that in premature infants rickets can develop even when the calcium and inorganic-phosphorus concentrations fall within the ranges regarded as normal for full-term infants. (For Sydow's findings on these levels, see p. 328.)

The product of the calcium and phosphorus levels was believed by Howland and Kramer (158) to be the determining factor in calcification of the bones. In their series they found that all infants in whom the product was less than 30 mg. per 100 cc. of serum had active rickets and all those in whom this product was 40 or more had healing rickets; a few infants with active rickets were in a borderline group in which the product was between 30 and 40. Eliot and Park (97, p. 38) point out that this formula does not have independent value for diagnosis, citing as illustration the case of a premature infant that had marked rickets and a calcium-phosphorus product of 64. They believe that the rate of bone growth, especially rapid in premature infants, influences the concentration of calcium and phosphorus necessary for calcification.

The level of **phosphatase** in the serum is also an aid in the diagnosis of rickets, for the level is usually elevated in this disease. In healthy children the phosphatase level is 5 to 15 Bodansky units per 100 cc., according to Bodansky and Jaffe (42). Barnes and Munks (30) give the average level of phosphatase in the serum of 33 healthy infants 2 to 6 weeks of age as 10.4 Bodansky units (standard deviation, ± 3.05). In mild rickets, according to Bodansky and Jaffe, the phosphatase level is about 20 or 30 units; in marked rickets, about 60 units; and in very marked rickets, above 60 units. (For effect of type of feeding on the phosphatase level see p. 328.)

Sydow (344, pp. 18, 20, 50, 62) has made a comprehensive report of the serum calcium, inorganic-phosphorus, and phosphatase levels in relation to rickets in premature infants. He made serial serum-calcium, serum-inorganic phosphorus, serum-phosphatase, and serumprotein determinations and roentgenographic examinations of the wrists of 118 premature infants weighing 1,010 to 2,000 gm. at birth "who were considered able to be subjected to the necessary examination without risk." These infants were followed up to 6 months of age. Three groups of normal full-term infants (total number, 292) weighing more than 3,000 gm. at birth served as controls-one group examined during the first week and the other two, at 2 weeks to 6 months of age. The diets of the infants were human milk or cow's milk with and without supplements of vitamin D. The groups of infants receiving supplements of vitamin D on which the statistical analysis of blood-serum determinations was based consisted of those who had received at least 25 daily doses of 5,000 to 10,000 international units of D_3 or a single massive dose of 500,000 international units of D_2 given at least 25 days before the serum determinations to test the effect of the vitamin

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were begun; the earliest of these determinations were therefore made at the age of 31 days.

In the first days of life the premature infants had about the same serum inorganic phosphorus as the full-term infants; their serum phosphatase was higher and their serum calcium and serum protein, lower. After this early period these values were influenced by the type of milk feeding and whether or not vitamin D was given. Serum calcium was found to be low in premature infants whether fed human milk or cow's milk but was much higher when vitamin D was added to either. When cow's milk was fed, without vitamin D, serum inorganic phosphorus was higher than in premature infants fed human milk alone but not quite so high as in the full-term group. Serum phosphatase was lower in the premature infants fed cow's milk alone than in the infants fed human milk alone, but it was significantly higher than in the full-term group. When premature infants were given cow's milk plus vitamin D the serum-phosphatase level was normal and was significantly lower than in any other group of premature infants, though it was probably a little higher in the birth-weight group 1,510 to 1,750 gm., than in the group 1,760 to 2,000 gm. (344, pp. 60-72).

Relation between laboratory and roentgenographic findings

In Sydow's study (344, pp. 101–105), among infants 31 to 105 days of age for whom the roentgenographic findings were normal, the serumcalcium level in most cases ranged from 9 to 11 mg. per 100 cc., irrespective of the type of feeding and whether or not vitamin D was given. When signs of rickets were present the range for most of the infants who had been given no vitamin D was 8.0 to 10.0 mg., but in some cases the value was as low as 6.4 mg.; for infants who had been given vitamin D the values were the same as for infants in whom the roentgenographic findings were normal.

Among infants with normal roentgenographic findings the phosphorus level was above 4 mg. per 100 cc. in almost all cases, and values of less than 4 mg. were therefore regarded by the author as indicating rickets. Rickets may be present, however, even if the level is higher than 4 mg.; among infants showing roentgenographic signs of rickets, a little less than half of those fed human milk had levels below 4 mg., and almost all of those fed cow's milk had levels above 5 mg.

Almost all the infants whose roentgenograms were normal had serum-phosphatase levels of 11 to 30 units, and none exceeded 40 units, irrespective of type of feeding. The author concludes, therefore, that a value of more than 35 units in a premature infant "may certainly be considered as indicating rickets." When roentgenographic signs of rickets were present in infants given human milk the phosphatase level in most cases was above 30 units and in almost all cases was above 20 units. When roentgenographic signs of rickets were present in infants fed cow's milk, most values were lower than 30 units and some were extremely low.

TREATMENT

Sunlight, ultraviolet light, and vitamin D in various forms are effective in healing active rickets. There is a direct relationship between the amount of vitamin D given and the rapidity with which healing of the rachitic process occurs. A prophylactic dose of vitamin D is curative but will require a longer time to effect healing than will a larger dose.

The commonest forms of vitamin D, in addition to cod-liver oil, are viosterol (D_2 , activated ergosterol, calciferol) from vegetable sources and activated 7-dehydrocholesterol (D_3) of animal origin, occurring naturally in various fish oils. It may be given orally in the form of fish oil, fish-oil concentrates, or viosterol in oil. Fish-oil preparations have the advantage that they contain vitamin A as well as vitamin D, but they should not be given to small premature infants because of the danger of aspiration, resulting in lipoid pneumonia. (See Infection, p. 256.) For premature infants, particularly in the period when the swallowing reflexes are relatively inactive, a vitamin-D concentrate miscible in water or milk should be used. Concentrated vitamin D may also be given parenterally or orally in massive doses at monthly or longer intervals. (See Nutrition, p. 178.)

monthly or longer intervals. (See Nutrition, p. 178.) The dose of vitamin D required by premature infants suffering from rickets has not been established. It is generally believed that premature infants require larger doses of vitamin D than do full-term infants, both for prophylaxis and for therapy. Park (252) believes that it is possible in most cases to cure rickets with a daily dose of 1,000 units of vitamin D but that with premature infants 10,000 to 20,000 units or more daily may be necessary to terminate the disease in a short time, after which the preventive dose should be given. Jeans and Marriott (171, p. 434) suggest that for fairly rapid healing and therefore for a relatively short period, the full-term infant with active rickets be given daily 3 teaspoonfuls of a high-potency cod-liver oil (800-900 units to the teaspoonful), or 20 drops (4,000 units) of viosterol, which, in common with all highly concentrated forms of the vitamin, they say, is utilized less efficiently. For the premature infant with active rickets no amount is specified. Jeans does not consider that there is satisfactory evidence that the premature infant requires a larger dose than the full-term infant. (Personal communi-cation from P. C. Jeans, M. D., Children's Hospital, Iowa City.)

The effectiveness of the therapeutic dose decided upon and the period for which it is needed should be determined in each case by clinical signs which are often apparent, by roentgenographic evidence of deposition of calcium, and finally by the calcium and inorganic-phosphorus levels of the blood serum. Park (252) says: "If the level of the calcium is normal and the inorganic phosphorus rises to 5 mg. per 100 cc. or above, one knows that a curative effect has been obtained." If the desired therapeutic effect has not been obtained the dose can be increased, according to Park, 1,000, 2,000, or 5,000 units at a time. However, if laboratory facilities for the blood tests are not available, Park says that any large dose should be reduced to 1,000 units after 10 days or 2 weeks and kept at that level for several months. (Personal communication from Edwards A. Park, M. D.) He warns (252): "For small premature babies I believe that signs of overdosage ought to be watched for [Sulkowitch test showing abnormal amount of calcium in the urine] if more than 20,000 units is given daily for more than 2 weeks."

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A single massive dose of 600,000 international units of vitamin D has been reported to result in rapid healing without ill effects. Such

a massive dose may be of special value if the rickets is associated with complications that make rapid healing of primary importance.

PREVENTION

It is the responsibility of the physician to institute measures to prevent rickets in all premature infants. Newer knowledge of methods of treatment offers more hope of preventing the disease. The important points to remember are that the antirachitic vitamin must be started in the first week of life, must be given in adequate doses and in a form that is safe for premature infants and that will be absorbed, and must be continued throughout infancy.

(For discussion of prophylaxis of rickets see Nutrition, p. 178.)

Tetany

Tetany is a state of neuromuscular irritability resulting from hypocalcemia. Tetany may occur in the early neonatal period, usually in the first week after birth. This type of tetany is probably the result of physiologic hypocalcemia associated with transient hypoparathyroidism. The type of tetany that occurs after the neonatal period is usually associated with rickets and is the result of vitamin-D deficiency. Guild (134) states that tetany usually does not occur until after the third month, but that premature infants show a special liability to tetany and in them the condition may occur earlier than in full-term infants.

TETANY OF NEWBORN INFANTS

Cause

The cause of tetany in the first week of life is not thoroughly understood. Smith (322, p. 227) explains the mechanism thus: "It appears that whereas the calcium of the blood declines during the first few days after birth, the phosphorus rises, so that very little change takes place in the product of the two figures. It is obvious that the postnatal variations in these minerals are, although under reasonably accurate control, nevertheless in a direction which would lead toward tetany, and indeed tetany has been more common in the neonatal period than has rickets." This has been considered due to a transient hypoparathyroidism. The blood calcium tends to rise about the third day. Bakwin (28) considers that cow's milk (with high phosphorus content) given in the early neonatal period tends to increase the likelihood of tetany because the rise in phosphorus tends to depress the calcium in the serum.

Diagnosis

Clinical symptoms of tetany in this period are twitchings or convulsions. Laryngospasm and carpopedal spasm may be present. Chvostek's sign (contraction of the facial muscles when the portion of the cheek in front of the ear is tapped) and Erb's sign (electrical reactions) are not helpful in the diagnosis of tetany of the newborn. The diagnosis depends on excluding other causes of convulsions, particularly intracranial birth injury and hypoglycemia, and on the finding of a low serum calcium (below 7 mg. per 100 cc.). The serumphosphorus level is usually high and the phosphatase level normal.

Treatment

Administration of calcium intravenously brings about a dramatic disappearance of symptoms, according to Anderson (23, p. 237). For full-term infants she advises 5 to 10 cc. of calcium gluconate in 10-percent solution given intravenously, followed by oral administration daily for a week or so of 2 to 3 gm. of a 10-percent calcium-chloride or calcium-lactate solution. For premature infants, when it is necessary to continue calcium therapy, smaller doses in more dilute solutions should be given. The 10-percent solution of calcium chloride should be further diluted by adding it to the milk feedings. It should not be given by gavage. Durlacher, Harrison, and Darrow (93) found that in three newborn infants observed by them, necrosis and ulceration in the gastrointestinal tract resulted from administration of calcium-chloride solution by gavage.

Guild advises against the use of parathyroid extract in the treatment of tetany of the newborn, because it has a depleting effect upon stored calcium, and because the condition is transitory and responds readily to treatment with calcium salts. (Personal communication from Harriet G. Guild, M. D., Johns Hopkins Hospital, Oct. 1947.)

TETANY DUE TO VITAMIN-D DEFICIENCY

Cause and relation to rickets

Guild (134) points out that "although only a very small percentage of infants with rickets have tetany, practically every infant with tetany has rickets . . ." Siwe (320) reports that a re-examination of the problem of the relation between rickets and tetany leads him to conclude that there is no direct relation between these associated conditions. The common factor is a generalized metabolic disorder caused by vitamin-D deficiency. Infections, to which premature infants are peculiarly liable, may be a factor in the transition from latent to active tenany, according to Guild (134).

Diagnosis

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Clinical symptoms of active tetany are hypertonicity, muscular twitching, carpopedal spasm, laryngospasm, and general convulsions, occurring separately or in combination. A positive Chvostek's sign in a full-term infant after 1 month of age is usually significant, but in premature infants neither Chvostek's sign nor Erb's sign can be depended upon for diagnosis up to 2 or 3 months of age.

If low serum calcium (below 7 mg. per 100 cc.) is associated with clinical symptoms the diagnosis of active tetany is definite. If low serum calcium is associated with a positive Chvostek's or Erb's sign latent tetany may be present even if clinical symptoms are slight or lacking. The serum inorganic-phosphorus level may be low or normal; the serum-phosphatase level, high.

Tetany that is due to vitamin-D deficiency must be differentiated from tetany due to alkalosis, which occurs as the result of conditions that cause imbalance of the various chemical constituents of the blood. For example, tetany may be of gastric origin when excessive vomiting causes loss of chloride in the serum, elevation of the bicarbonate, and increase in the carbon dioxide and pH of the blood. (See Acidosis, p. 310.) It may also occur as the result of administration of sodium bicarbonate. The convulsions of tetany must be differentiated particularly from those due to intracranial injury at birth and to various forms of meningitis. Except for the type that occurs in the early neonatal period, tetany due to parathyroid deficiency is rarely seen in infants.

Treatment

When clinical signs that suggest tetany occur in a premature infant, the life of the infant may be dependent on the correct diagnosis and on treatment as soon as the diagnosis is made or suspected. Treatment consists in the administration of calcium by mouth or parenterally depending on the severity of the symptoms. When very rapid relief of symptoms (convulsions or laryngospasm) is required calcium gluconate (5–10 cc. of a 10-percent solution) may be given intravenously, followed by calcium chloride by mouth, not by gavage. It is usually not necessary to give more than the one intravenous dose of calcium gluconate. Unfavorable results have followed the administration of calcium gluconate intramuscularly and of calcium chloride intravenously.

Calcium chloride is the most effective of the calcium salts for continued use, according to Guild (134). In active tetany, if it is used from the beginning, the initial dose for premature infants is 1 to 2 gm. in a 10-percent solution, which should be further diluted. (See p. 331.) This should be followed by $\frac{1}{3}$ to $\frac{1}{2}$ gm. at 4- to 6-hour intervals for the first 24 hours. After that, the same dose three or four times a day usually suffices to keep the symptoms under control, although it must be continued for at least 2 weeks and sometimes longer, while the antirachitic treatment is getting under way. When the tetany is latent it is not necessary to start with such a large initial dose. (Personal communication from Harriet G. Guild, M. D., Johns Hopkins Hospital, Baltimore.)

The administration of an acid has been found to be effective in increasing, by ionization, the utilization of the calcium already present in the blood serum. For this reason Nelson (244) says that small amounts of dilute hydrochloric acid may be added to the calcium chloride.

Any one of the antirachitic agents will cure tetany, but they require a longer time than calcium therapy to raise the level of the blood calcium. Both calcium therapy and antirachitic treatment should be used, according to Guild (134), in any case of tetany, the antirachitic treatment being started after the active symptoms of tetany have been brought under control by calcium therapy alone for a day or two. (For treatment of rickets in premature infants, see p. 328.)

Prevention

Prophylactic administration of vitamin D is the means of protection against postneonatal tetany, as well as against rickets.

Summary

RICKETS

Rickets, a disturbance in the calcium and phosphorus metabolism due to deficiency of vitamin D, tends to develop earlier, to progress more rapidly, and to be more severe in premature infants than in fullterm infants. This tendency is due to deficient antenatal storage of calcium, poor mineralization of the skeleton, rapidity of growth, inefficient utilization of calcium, phosphorus, and fat, deprivation of sunlight, and frequency of infection and of diarrhea.

The diagnosis of rickets may be made from clinical signs, from roentgenograms, and, most reliably, from determination of calcium, phosphorus, and phosphatase concentrations in the blood.

The diagnosis of rickets is difficult to make from clinical signs in premature infants. Craniotabes and evidences of tetany may be the first signs of the disease.

The early roentgenographic changes due to rickets are also difficult to detect and to interpret. They are not pathognomonic of rickets and must be differentiated chiefly from those due to scurvy or to syphilis. Early rachitic changes are usually seen in the cortex and the periosteum rather than at the cartilage-shaft junction, according to Eliot and Park. The changes may be atrophic (the thinning or absence of cortical shadows) with bone destruction greater than bone formation, or hypertrophic (thickening of the cortex), with slight and ineffective healing tendency. Periosteal encasements may be visible in the hypertrophic type.

"Periosteal proliferation" along the diaphysis of the long bones is considered by one investigator to be the earliest roentgenographic sign of rickets in premature infants. This sign was less frequent the larger the amount of vitamin D given, and when it did appear, subsequent roentgenographic signs of rickets were negligible among the infants given the largest amounts of vitamin D. This investigator did not confirm his roentgenographic diagnoses by determinations of serum calcium and phosphorus.

After a recent comprehensive study of rickets in premature infants Sydow concluded that the earliest roentgenographic sign is metaphyseal decalcification, which usually appeared in the first month of life and was usually followed by the accepted roentgenographic signs.

Later roentgenographic evidences of rickets appearing at the cartilage-shaft junction—listed by Eliot and Park as cupping, spreading, spur formation, fringing, and stippling—are the same in premature infants as in full-term infants. They are best interpreted from serial films.

Sydow found that more than half of the roentgenograms of premature infants over 1 month of age showed evidences of rickets, active or healed, as interpreted by Eliot and Park, and a very few roentgenograms of infants under 1 month of age showed such evidences.

The most accurate method of diagnosing early rickets in premature infants is determination of the serum calcium and inorganic-phosphorus levels. In infants with rickets the serum calcium is usually within normal limits and the phosphorus low; but in premature infants the calcium level may be somewhat reduced and the phosphorus level very low, or both may be within normal limits. In rickets accompany-

ing tetany the serum calcium and not the phosphorus may be reduced. A serum-calcium and phosphorus product of less than 30, sometimes considered diagnostic of rickets, is believed by Eliot and Park not to have independent value for diagnosis, especially for rickets in premature infants, because it does not take their rapid rate of bone growth into consideration.

An increase in the level of serum phosphatase may be helpful in confirming the diagnosis of rickets. In mild rickets in infants it is increased from the normal average of 8.9 Bodansky units to 20 or 30 units; in marked rickets, to about 60 units; and in very marked rickets, to more than 60 units.

Sydow made determinations of calcium, phosphorus, phosphatase, and protein levels in the blood serum, as well as roentgenograms, of his series of premature infants and of control groups of full-term infants. Shortly after birth the premature infants had about the same serum inorganic phosphorus as the full-term infants; their serum phosphatase was higher and their serum calcium and serum protein, lower. Later values were influenced by whether they were fed human milk or cow's milk and whether or not they were given vitamin D. When roentgenographic findings were normal, in most cases the calcium level ranged from 9 to 11 mg. per 100 cc., the phosphorus level was above 4 mg. per 100 cc., and the phosphatase level ranged from 11 to 30 units. When roentgenographic signs of rickets were present the calcium levels for most infants given no vitamin D ranged from 8.0 to10.0 mg. but were normal for those given vitamin D; phosphorus levels in a little less than half of those fed human milk were below 4 mg. and in almost all those fed cow's milk were above 5 mg.; and phosphatase levels in infants fed human milk were almost all above 20 units and most were above 30, whereas in infants fed cow's milk most levels were below 30 and some were extremely low.

Sunlight, ultraviolet light, and vitamin D in various forms are effective in healing active rickets, the rapidity of healing depending upon the amount of vitamin D made available. For smaller premature infants a vitamin-D concentrate miscible in water or milk or a massive dose may be given, as premature infants are believed to require larger amounts than do full-term infants. Park believes that rickets may be cured with daily doses of 1,000 units, but that for premature infants 10,000 to 20,000 units or more may be necessary for a short time. The effectiveness of the therapeutic dose decided upon and the period for which it is needed must be determined in each case by clinical, roentgenographic, and chemical tests. A single massive dose of 600,000 units may be of special value in cases involving complications that make rapid healing of primary importance.

Antirachitic prophylaxis should be begun in the first week of life. Vitamin D should be given in adequate doses, in safe and absorbable form, and at regular intervals, and should be continued throughout infancy.

TETANY

Tetany is a state of neuromuscular irritability resulting from hypocalcemia. Premature infants may develop tetany in the first week of life, or after the neonatal period; they are especially susceptible to the postneonatal type and may develop it earlier than full-term infants do. The cause of tetany in the early neonatal period is not thoroughly understood. It is probably a physiologic hypocalcemia associated with transient hypoparathyroidism.

Evidences of tetany of newborn infants are twitching, convulsions, and sometimes laryngospasm and carpopedal spasm, in association with low serum calcium (below 7 mg. per 100 cc.). Chvostek's and Erb's signs are not helpful in the diagnosis. The convulsions of tetany need to be differentiated from those due to other conditions, particularly intracranial birth injury and hypoglycemia. The disease usually yields quickly to treatment with calcium salts. Treatment with parathyroid extract is not advised.

Tetany after the early neonatal period is due to vitamin-D deficiency. It is not evidence per se of rickets but is usually associated with rickets.

The diagnosis of active tetany due to vitamin-D deficiency is based mainly on the evidences mentioned for tetany of newborn infants. Positive Chvostek's and Erb's signs are not dependable evidence of active tetany in premature infants in the first 2 or 3 months, but if combined with low serum calcium they point to latent tetany, even when clinical symptoms are lacking. Postneonatal tetany must be differentiated from other conditions causing convulsions at this age, such as alkalosis, intracranial injury, and meningitis.

When rapid relief is necessary calcium gluconate (5-10 cc. of a 10percent solution) should be given intravenously followed by calcium chloride by mouth. When calcium chloride is used from the beginning the initial dose recommended for premature infants is 1 to 2 gm. of a 10-percent solution; this is followed by smaller doses for at least 2 weeks. The calcium-chloride solution should be given in the milk feeding, not by gavage. After a day or two of calcium therapy alone, when the symptoms of active tetany have been controlled, antirachitic therapy should be started.

As with rickets, the means of prevention is administration of vitamin D.

OTHER CONDITIONS Retrolental fibroplasia

Terry (346) was the first to report an eye condition apparently related to extreme prematurity to which he gave the name retrolental fibroplasia. This disease entity consists, according to Terry (347), "in primary and secondary changes related to: (1) persistence of all or part of the hyaloid-artery system; (2) growth of embryonic connective tissue behind the lens; (3) persistence or overgrowth of fibrillar structure of vitreous. These changes appear to arise from hypertrophy and perhaps even sclerosis of the persistent hyaloid artery and tunica vasculosa lentis."

CAUSE

In his first report of this condition, which Terry then described as a "fibroblastic overgrowth of persistent vascular sheath behind each crystalline lens," he raised the question whether it was due to persistence of fetal structures or to an abnormal membrane that grows after birth "since it has no exact counterpart in the normal fetal development of the eye."

In later reports Terry discussed various theories of causation but found himself unable to make a conclusive statement. In his last article (351), briefly reviewing the ground that had been covered by his studies, he says: "None of the various classes of etiologies can be absolutely excluded. These include heredity, those causes operating before birth, those arising through premature separation from maternal hormones, the precocious functioning of systems such as the respiratory, digestive, and cardiovascular, the heat regulatory center, and those arising through precocious exposure to light. It appears that a common exciting factor is related to premature birth and incubator life. It seems logical that, of the etiologies limited to the eyes alone, precocious exposure to light is still the leading factor in the cause of ocular developmental abnormalities, yet no clinical or experimental finding strongly supports this. Heredity seems least likely. To know whether we are studying one disease entity or several which have similar clinical features but different causes would more clearly define our problem."

Warkany and Schraffenberger (388) and Jackson and Kinsey (168) have produced retrolental fibrotic changes in rats' eyes by feeding the mothers diets deficient in vitamin A. Jackson and Kinsey, however, found that the eye defects did not appear unless the maternal deficiency of vitamin A was extremely severe. They commented: "To the extent that the physiologic processes associated with reproduction in human beings parallel those in the rat it may be inferred that vitamin-A deficiency in the mother is not a probable cause of retrolental fibroplasia." Terry (168), in discussing Jackson and Kinsey's report, stated that "pediatricians working on the problem of retrolental fibroplasia found clinically that this abnormality

. . . has developed in two infants whose vitamin-A blood level was kept normal by therapeutic measures."

INCIDENCE

Terry (350) commented as follows on the incidence of retrolental fibroplasia: "In 1941 it was recognized that a massive growth of embryonic connective tissue occurring in the meshwork of a persistent tunica vasculosa lentis is linked with prematurity. To my knowledge there are at least 162 cases at the present time. Doctor Stewart Clifford has found that [at the Boston Lying-In Hospital] 12 percent of the infants weighing 3 pounds (1,360 gm.) or less at birth develop this disease. This percentage, based on less than 50 cases of prematurity, can be considered only a trend. If the true percentage of infants developing this disease is about 10, approximately 600 cases are to be expected in this country each year, which, if some prophylaxis is not found, will add materially to the 175,000 blind."

Cases of retrolental fibroplasia in premature infants were reported to Terry by a number of ophthalmologists, but no data on a countrywide basis are available as to the incidence of the disease.

DIAGNOSIS

The condition described as retrolental fibroplasia occurs usually in very small premature infants. The six cases described by Terry (348) (case 7 he later said (349) should be disregarded) ranged in weight from 2 lb. to 3 lb. 11 oz., three weighing less than 3 lb. The characteristics of this condition described by Terry are based

The characteristics of this condition described by Terry are based on his own observations and reports of others. The symptom that usually causes the parents to bring the child to a physician is poor vision, usually noted at about 6 months of age. Examination shows one or more of the following abnormalities: jerky, irregular, and somewhat searching nystagmus; photophobia, manifested by a tend-



NORMAL EYE

DISEASED EYE

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Figure 31.—Diagram of (a) the normal eye and (b) the changes that are the result of retrolental fibroplasia (from Homer, William F., Jr.: "The Eyes Have It." Hygeia, Feb. 1946).

ency to rub the eyes when in the light; microphthalmus; fetal-blue color of the iris; small size of eyes. Ophthalmoscopic examination reveals a grayish-white, opaque membrane behind the crystalline lens of both eyes; thin ciliary processes in front of the opaque tissue; a persistent hyaloid artery; and often retinal separation. (See fig. 31.)

The pathology of this condition is described by Terry as follows: A mass of embryonic connective tissue is found behind the lens, the ciliary processes are distorted, the retina is "far forward on the ciliary body," and there is evidence of persistence of the hyaloid artery. In some cases with unilateral involvement intraocular hemorrhage and inflammation were found in the embryonic connective tissue.

Retrolental fibroplasia must be differentiated from two eye diseases—retinoblastoma and congenital cataract. These conditions are usually present at birth but may not be apparent until later in infancy or childhood, whereas retrolental fibroplasia is usually not seen until the fifth or sixth month. The diagnosis should be apparent on ophthalmoscopic examination—a tumor with a yellowish tinge in retinoblastoma and a circumscribed opacity, usually centrally situated under the anterior capsule of the lens, in congenital cataract. An expert ophthalmologist should be consulted when one of these three conditions is suspected.

TREATMENT

Terry (350) considers that surgical, radiation, and diathermy therapy have proved on the whole unsuccessful. A surgical attempt, however, to establish a new vascularization of the ciliary body with the episclera is being made with some beneficial results.

To prevent the most common complications—glaucoma and posterior synechia—Terry suggests the use of miotics and mydriatics: to prevent glaucoma, a miotic daily, and to prevent posterior synechia, a combination of powerful mydriatics weekly which will be effective for only a few hours.

PROGNOSIS

The prognosis in these cases appears to be poor, as most of the infants have become partly or totally blind. Terry (349) states that "partial resolution of the fibroplastic tissue in the eyes in which growth does occur when no complications arise rarely results in improvement sufficient to permit good vision."

Noninfectious skin conditions

There are several conditions that affect the skin and subcutaneous tissues that are peculiar to the infant in the neonatal period. There is some confusion in the terminology of these different conditions. Wright (403) classifies them as "disturbances in the subcutaneous fat" and includes among them subcutaneous-fat necrosis, sclerema neonatorum, edema neonatorum (sclerema edematosum), scleroderma (hide-bound disease). Holt and McIntosh (155) use, under the general heading "miscellaneous conditions" of the skin, the terms sclerema; pseudosclerema or "subcutaneous fat necrosis of the newborn"; scleredema; and scleroderma.
Sclerema and scleredema are rare conditions that may occur in premature infants; pseudosclerema (subcutaneous fat necrosis) occurs in healthy, well-nourished infants. Scleroderma is an obscure disease that may occur at any time of life but occurs rarely in infancy.

Sclerema neonatorum is characterized by intense induration of the subcutaneous tissues which, starting on the buttocks, thighs, or trunk, may spread rapidly to other parts of the body. It is accompanied by local as well as general circulatory disturbances. Holt and McIntosh consider that this induration is due chiefly to solidification of the subcutaneous fat. They consider that one factor in the production of sclerema is a peculiarity in the newborn infant's fat which contains less olein and thus has a higher melting point than adult body fat. Low skin temperatures in infants may thus cause the fat to solidify. Other and unknown factors are concerned, however, they point out, because "microscopic and chemical examinations of the subcutaneous tissues of normal and sclerematous infants of the same age have not revealed any striking differences."

Wright describes the skin as "reddish, purplish or mottled, hard, rigid, and cold." The rigidity usually progresses accompanied by feeble respirations, weak pulse, and subnormal temperature.

Treatment is directed toward maintaining body temperature and nutrition. No specific treatment for sclerema is known, however, and the prognosis is very poor.

Scleredema is a severe form of edema, hard and brawny, accompanied by general symptoms similar to those of sclerema but without circumscribed lesions. It has no relation to the relatively mild edema often seen in premature infants in the neonatal period. Scleredema is usually seen first on the feet and may spread to involve nearly the whole body. No specific treatment is known and the prognosis is poor.

Diarrhea

Premature infants are very prone to diarrhea. The diarrhea may develop gradually, starting with a slight increase in the number or a slight change in the consistency of the stools, or it may be sudden and explosive, with loose, watery stools. Nurses should enter on the nursing chart, each time the diaper is changed, the character of the stool and the hour at which the stool is noted and should report at once to the physician any change in frequency or character of the stool in order that he may institute appropriate treatment early. Frequent stools may be evidence of a digestive disturbance or of infection, enteral or parenteral. True diarrhea is a much more serious condition in a premature infant than in a full-term infant.

The general principles involved in the treatment of diarrheal conditions are:

- 1. The infant should be placed in a separate room (observation unit) and isolation precautions should be taken.
- 2. Feedings by mouth should be discontinued; they should be resumed with caution as the diarrheal condition permits.
- **3.** Fluid requirements should be maintained with parenteral administration of appropriate fluid to prevent dehydration and acidosis.

If the diarrhea is a mild one it will usually respond to treatment within 24 to 48 hours provided there is no serious underlying pathology. If the diarrhea is not arrested or tends to become more severe, premature infants tend to develop rapidly dehydration and acidosis, evidenced by apathy or restlessness. These symptoms are indication of serious changes taking place in the body due to loss of fluid and electrolyte, and appropriate treatment must be carried out quickly if the infant's life is to be saved.

Parenteral administration of fluid and electrolyte—so-called "replacement therapy"—requires hospitalization of these infants because chemical blood studies before and during treatment are necessary. The carbon-dioxide serun content should be determined, as well as the chloride, nonprotein-nitrogen, and potassium levels. Many hospitals, however, will not be equipped to make these studies. If this is the case, fluids for subcutaneous and intravenous therapy, such as Ringer's or Hartmann's "combined" solution, may be used with a fair amount of assurance that the electrolyte balance will not be disturbed. Transfusions of whole blood or plasma also are usually indicated in these cases to increase blood volume as well as salt and protein content.

The clinical evidences, diagnosis, and treatment of the conditions of which diarrhea is a symptom, and also replacement therapy, are discussed in the section Infection, page 262.

Summary

RETROLENTAL FIBROPLASIA

Retrolental fibroplasia is an overgrowth of fibrous tissue on the posterior aspect of the lens of the eye. The cause of this condition is not known. The condition has been produced experimentally in animals placed on a diet deficient in vitamin A.

Retrolental fibroplasia usually is found in premature infants weighing less than 1,500 gm. at birth (about 3 lb.). It occurs rarely in larger premature infants and in full-term infants. The incidence of retrolental fibroplasia has not been determined, but it has been estimated, on the basis of a small number of cases, that about 10 percent of the infants weighing 3 lb. or less suffer from this condition.

The diagnosis is usually not made until the parents note that the infant has poor vision. Other symptoms are nystagmus, photophobia, and microphthalmus. Examination of the eyes reveals fetal-blue color of the iris and a grayish-white opaque membrane behind the crystalline lens. The membrane is composed of embryonic connective tissue; the ciliery processes are distorted; the retina is displaced; and there is persistence of the hyaloid artery. The condition must be differentiated from retinoblastoma and congenital cataract, which are usually present shortly after birth.

Treatment of retrolental fibroplasia is merely palliative and does not offer hope of saving the infant's vision.

NONINFECTIOUS SKIN CONDITIONS

Sclerema and scleredema are rare conditions that may occur in the neonatal period. In sclerema induration of the skin and subcutane-

ous tissues appears shortly after birth accompanied by circulatory disturbances. In scleredema there is a hard, brawny, generalized edema, with general symptoms also. Treatment in both these conditions is nonspecific. The prognosis is poor.

DIARRHEA

Premature infants are very liable to develop diarrhea. Frequent or loose, watery stools may be evidence of a digestive disturbance or of enteral or parenteral infection.

The infant should be isolated; oral feedings should be discontinued; and fluid requirements should be maintained by parenteral administration. Dehydration and acidosis must be guarded against. If they develop they should be treated with appropriate solutions. Transfusions of blood or plasma are usually indicated in severe cases of diarrhea.



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"The expulsion of a nonviable product of conception occurring before the seventh lunar month or $6\frac{1}{2}$ calendar months (twenty-eighth week) of gestation is considered an abortion."²

Even where the recommended distinction between a live-born and a stillborn infant has been accepted, infants who do not breathe but whose hearts are beating at birth may sometimes be certified as stillborn, particularly if a stethoscope is not used to detect the heartbeat. If an infant's heart beats, no matter for how short a time, he should be certified as live-born, according to the foregoing definition.

The distinction between an abortion, a premature birth, and a fullterm birth on the basis of estimated period of gestation is not a clear-cut Stander ³ points out: one.

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last menstrual period, so that the actual duration of pregnancy is 270 davs or less. This rule, however, is subject to many exceptions, as apparently well-developed children may be born as early as the two hundred and fortieth and as late as the three hundred and twentieth day after the last menstrual period."

The distinction between an abortion and a live-born premature infant has caused considerable confusion, because an infant sometimes lives when the gestation period has been estimated as less than 28 weeks. If such an infant shows any "signs of life" after birth, the birth should be certified as a live birth regardless of the estimated period of gestation and regardless of the time after birth that signs of life persist.

Certification of death

On the standard certificate of death (facing p. 365), the physician is asked to certify the "immediate cause of death" (item 21) and the underlying or contributory cause (in the space headed "due to" on the certificate). The Bureau of the Census has defined these terms 4 as follows:

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"The disease entity which initiates the series of disease entities resulting in death will be known as the underlying cause of death. When there is only one disease entity present, the underlying cause of death and the immediate cause of death are considered to be identical. The underlying cause of death should be written in the space following the words due to and should be stated in reverse order of occurrence from the immediate cause of death."

The information from death certificates is tabulated by the National Office of Vital Statistics using the international list of causes of death and the joint-cause list.⁵

Those sections of the international list of causes of death that apply to causes of death of premature infants under 1 year of age are contained in the tabular list, groups XIV and XV, numbers 157-161.

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 - c. Anencephalus.
 - d. Other congenital malformations of the central nervous system.
 - e. Congenital malformations of the heart.
 - f. Other congenital malformations of the cardiovascular system.
 - g. Congenital malformations of the digestive system.
 - h. Congenital malformations of the genitourinary system.
 - m. Other and unspecified congenital malformations.

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XV. Diseases peculiar to the first year of life.

158. Congenital debility (cause not stated).

- 159. Premature birth (cause not stated).
- 160. Injury at birth.
 - a. Intracranial or spinal hemorrhage.
 - b. Other intracranial or spinal injuries.
 - c. Other injuries at birth.
- 161. Other diseases peculiar to the first year of life.
 - a. Asphyxia (cause not specified), atelectasis. (See p. 49 for clinical diagnosis.)
 - b. Infection of the umbilicus; pemphigus and other infections (nonsyphilitic).
 - c. Other specified diseases peculiar to the first year of life.

All other causes of death of premature infants, such as syphilis and tuberculosis, are found under their respective headings in the index and the tabular list.

For statistical purposes the National Office of Vital Statistics tabulates only the immediate, or primary, causes of death. Premature birth (title 159) is accepted as a primary cause of death only when it is certified as the *sole cause* or when the other cause reported is vague or ill-defined. When two or more causes of death are certified, the cause to be classed as primary for statistical purposes will be determined according to the rules of the Manual of Joint Causes of Death, regardless of whether this cause was entered by the attending physician as immediate or contributory. For example, if the physician certifies injury at birth (160) and premature birth (159) as the causes of death of an infant under 1 year, the National Office of Vital Statistics will classify this death as due to injury at birth, since title 160 (injury at birth) takes precedence as a primary cause of death over title 159 (premature birth). If, on the other hand, the physician certifies premature birth and certain ill-defined conditions such as are listed under titles 158 and 161, premature birth takes precedence as the primary cause of death.

It should be pointed out that the tabulations of the National Office of Vital Statistics, in accordance with the international list rules of classification, do not show the total number of premature infants that die; they show only the number of infants that are reported to have died from premature birth the cause of which is not stated and those that are specified as premature and are reported to have died of some ill-defined condition that according to the joint-cause classification does not take precedence over premature birth. It is very important that the physician enter on the death certificate the cause of death of a premature infant in as specific terms as possible and that he enter also the month of gestation in the space provided for that purpose. More care in filling in death certificates for premature infants would provide the National Office of Vital Statistics with data that would enable it to produce additional information, such as cause of death by period of gestation. Information on period of gestation is frequently omitted from the death certificate.

Appendix 3

STAGES AND SEQUENCES OF DEVELOPMENT '



¹Gesell, Arnold; and Amatruda, Catherine S.: Developmental Diagnosis: Normal and abnormal child development. 2d ed. New York: Hoeber, 1947. 496 pp. 366



Figure II.—DEVELOPMENTAL SEQUENCES OF MOTOR BEHAVIOR.

The items on this chart include both gross motor and fine motor behavior patterns. To ascertain the maturity of postural control we institute formal postural tests which reveal the repertoire of the infant's behavior: supine, prone, sitting, and standing.

Fine motor control is evaluated in a similar manner. Small objects such as cubes, pellet, and string elicit patterns of fine manual control.

Such tests illustrate the principles which also underlie the developmental diagnosis of behavior in the adaptive, language, and personal-social fields.



Figure III.—DEVELOPMENTAL SEQUENCES OF ADAPTIVE BEHAVIOR.

To determine how the infant uses his motor equipment to exploit the environment we present him with a variety of simple objects. The small red cubes serve not only to test motor coordination, they reveal the child's capacity to put his motor equipment to constructive and adaptive ends. The cube tests create an objective opportunity for the examiner to observe adaptivity in actionmotor coordination combined with judgment.

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Figure IV.—DEVELOPMENTAL SEQUENCES OF LANGUAGE BEHAVIOR. Language maturity is estimated in terms of articulation, vocabulary, adaptive use, and comprehension. During the course of a developmental examination spontaneous and responsive language behavior is observed. Valuable supplementary information may also be secured by questioning the adult (amiliar with the child's everyday behavior at home.

LEVELS	
MATURITY	
5 YEARS _	
4 YEARS _	Can wash and dry face. Goes on errands. Plays cooperatively.
3 YEARS _	
2 YEARS	/Verbalizes toilet needs. Plays with dolls.
18 MONTHS	/ Uses spoon with moderate spilling. Toilet regulated.
12 MONTHS _	/ Cooperates in dressing. Gives toy. Finger feeds.
40 WEEKS _	- / Plays simple nursery games. Feeds self cracker.
28 WEEKS	Plays with feet and toys. Expectant in feeding situations.
IS WEEKS	Plays with hands and dress. Recognizes bottle. Poises mouth for food.
4 WEEKS	Regards faces.
BIRTH _	
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Figure V.—DEVELOPMENTAL SEQUENCES OF PERSONAL-SOCIAL BEHAVIOR.

Personal-social behavior is greatly affected by the temperament of the child and by the kind of home in which he is reared. The range of individual variation is wide. Nevertheless maturity factors play a primary role in the socialization of the child. His social conduct is ascertained by incidental observation and by inquiry. The chart illustrates types of behavior which may be considered in evaluating the interaction of environmental influences and developmental readiness.
Appendix 4

SPECIFICATIONS FOR INCUBATORS

Prepared by National Bureau of Standards, U. S. Department of Commerce, and Children's Bureau, Social Security Administration, Federal Security Agency.

I. MATERIAL

- a. The frame, base, supports, legs, hood, case, and mattress holder of the incubator shall be of metal, wood, wood substitute, organic plastic, or other suitable material that does not warp, shrink, swell, buckle, age, or fatigue unduly under operating conditions.
- b. Windows shall be of shatterproof glass or other shatterproof, noninflammable, transparent material.
- c. Water containers shall be made of nonrusting material.
- d. The finish of the incubator and of any mattress holder shall be of metal, metal plate, or enamel, sufficiently smooth, hard, and durable to permit thorough and repeated cleaning.

II. SIZE

- a. The dimensions shall be sufficient to house the necessary equipment, with a clear space directly above the mattress of at least 23 in. in length, 13 in. in width, and 9 in. in height.
- b. Any mattress holder, or space for a mattress, shall be at least large enough to accommodate a mattress 23 in. in length and 13 in. in width.

Note 1. It is suggested that any mattress provided for use in or with an incubator should have an upper surface which is substantially a plane. No point on the upper surface shall be more than one-half inch below a straight edge laid on the upper surface of the mattress in any direction.

III. MECHANICAL DESIGN

- a. The incubator shall be constructed with such openings or windows in the top and sides as may be needed to afford at all times a clear view of the full length of the infant's face and the upper part of his chest by an attendant, whether sitting or standing, near the incubator.
- b. The type of incubator that is completely enclosed or more than semienclosed shall be provided with suitable doors, sliding windows, ports, or other openings, to permit con-

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¹ Except for slight revisions, these specifications are the same as the tentative ones published in Am. J. Pub. Health 30: 1415-1421, December 1940.

Premature Infants

venient servicing of the infant without undue change in environmental conditions.

c. The type of incubator that is a closed box or semihooded box designed to be set on a table, bench, or auxiliary base shall be provided, at opposite ends or sides, with a suitable type of handle in sufficient number to accommodate comfortably two hands at each end or at each side. These handles shall be of sufficient strength and so attached to the incubator as to sustain safely the weight of the entire incubator, necessary equipment, mattress, bedding, and an infant 6 lb. in weight.

Note 2. It is suggested that the type of completely enclosed incubator or more than semienclosed incubator that stands on the floor and is designed to be rolled, shifted, or moved should be equipped with at least one handle at either end to facilitate handling.

- d. The type of incubator that stands on the floor shall be equipped with a base, a stand, or well-braced legs, so spaced as to occupy an area of floor not less than 13 in. in width and 23 in. in length.
- e. The type of incubator that stands on the floor and is designed to be rolled, shifted, or moved shall be equipped with a sufficient number of freely rolling casters or wheels, with tires of rubber, rubber substitute, or suitable composition, the diameter of each caster or wheel, including the tire, to be at least 2 in.

Note 3. It is suggested that freely rolling wheels may require a brake as a safety precaution.

- f. The type of incubator that is designed to permit tilting of the upper part of the incubator without movement of the base, stand, or legs shall have a pivot axis across the center, with a clamp and guide at one end. The clamping handle shall be placed sufficiently high to permit the attendant to reach it without stooping.
- g. Water jackets, water tanks, and reservoirs shall be so constructed as to be readily cleaned, filled, and drained completely. They shall be equipped with a pilot light, warning light, protected water gauge, or other device, of such design as to facilitate the maintenance of an adequate supply of water. Water jackets shall be provided with suitable air vents to permit ease in filling and draining.
- h. The type of incubator that contains a water-jacketed compartment for the infant shall be provided with some means of preventing accidental flooding of the compartment.
- i. The types of incubators that are completely enclosed or are more than semihooded shall provide a system of ventilation that includes air inlets and outlets, motor-driven fans, or other necessary equipment or design that will enable the incubator to fulfil the following requirements, when the air temperature in the infant compartment does not differ from room temperature by more than 10° F.: The incubator shall be flooded with oxygen to not less than 50

percent excess oxygen (above normal) and then allowed to diffuse out by means of the normal operation of the ventilating system. Samples of the atmosphere in the infant compartment shall be tested at sufficiently frequent intervals to give a smooth curve for the return to usual atmospheric conditions. From this curve it shall be shown that the decrease from 40 percent excess oxygen to 20 percent excess oxygen takes place in not more than 10 minutes; or the result of an equivalent test, involving some other appropriate gas or material, shall show a decrease from 40 percent excess to 20 percent excess above usual atmospheric conditions within 10 minutes.

IV. ELECTRICAL EQUIPMENT

a. It is customary to provide an electrical ground connection for metal containers connected with ordinary 110-volt electric power or lighting circuits. The object is to protect persons coming in contact with the containers from being subjected to voltage higher than that of the local circuit, as may occur under some conditions. In an incubator so grounded it is possible that an infant might be subjected to a 110-volt potential, which would be dangerous or even fatal to the infant, although not generally dangerous to an adult.

For this reason it is strongly recommended that all electrically heated incubators be provided only with lowervoltage circuits, say 24 or 32 volts, for the operation of the devices which they contain. If this is done the metal case of the transformer, if used, should be provided with a ground connection in the approved manner for such equipment. But if 110-volt circuits are used for any purpose within the crib, the grounding should be omitted, regardless of possible danger to the attendant.

- b. A rubber-covered or similarly well-insulated waterproof cable or cord, at least 6 ft. long, having characteristics appropriate to the heater load, and with a standard prongtype plug, shall be attached to the incubator.
- c. All wires leading from the main-line switch to the heaters and other electrical equipment of the incubator shall be well insulated and fixed in position.

Note 4. It is suggested that the quality of the electrical equipment and wiring conform to the best practice as approved by the underwriters, to guard against fire hazards.

- d. A main-line switch shall be provided on the outside of the incubator at a convenient height. "On" and "off" positions of this switch shall be clearly marked. In addition, a pilot light shall glow in a conspicuous location whenever the cord or cable is attached to a proper electrical power supply and the main-line switch is in the "on" position.
- e. There shall be a clear indication of the proper voltage to be used, of whether current is direct or alternating, and of any other information essential to the proper choice of power supply. This information shall be posted on the incubator near the main-line switch.

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f. In any incubator designed for use with oxygen there shall be complete elimination of all sparking switches, sparking contacts, glowing coils, unprotected lamp bulbs, or like hazardous equipment. If any of this hazardous equipment is included in an incubator, a proper notice shall be conspicuously posted on the incubator to warn against use of that incubator with oxygen, or near an oxygen tent, or in or near an oxygen-rich or ether-rich atmosphere, or any other inflammable atmosphere.

V. TEMPERATURE AND HUMIDITY REGULATION

- a. The heater shall be of such a size, power output, and location in the incubator as to provide, with the help of any necessary controls, a top surface mattress temperature of as little as 5° F. above room temperature and also up to at least 15° F. above room temperature. To measure the top mattress surface temperature thermometers shall be placed on the mattress in thermal equilibrium with their surroundings and shall be covered with a 90 to 100 percent wool blanket about one-eighth inch in thickness or weighing about three-fourths ounce per square foot. The incubator heating system shall maintain a top surface mattress temperature such that thermometers, placed as described above, shall not differ in temperature from one another by more than 5° F. over a central area of 10 by 20 in. and shall fluctuate not more than 2° F. during operation at a given setting of the controls during room temperature fluctuations of as much as 10° F. in 6 hours. In the completely enclosed types of incubators the same limitations as to fluctuations shall apply also to the air temperature from 2 in. to 6 in. about and above the infant.
- b. One or more pilot lights shall be arranged either to show proper operation of the heater, or to give warning of failure of the heater, or both.
- c. A reliable and properly calibrated thermometer shall be so placed that its temperature is closely related to the mattress temperature. The enclosed, semihooded, and more than semihooded incubators shall in addition be provided with a reliable and properly calibrated thermometer so placed as to indicate the temperature of the air surrounding the infant.
- d. One or more thermostats as needed shall be so located as to insure compliance with the above limitations as to uniformity and fluctuation of mattress and air temperatures. These thermostats shall be adjustable without necessitating disturbance of the infant.
- e. In addition, a master thermostat shall be provided to open a main-line switch when either air or mattress temperature shall rise above a temperature of 101° F.

Note 5. It is suggested that a desirable development might be the location of some type of thermometer and thermostat within the space occupied by the mattress and near the infant to decrease the difference between the conditions immediately sur-

rounding the infant and those surrounding the thermometers and control devices.

- f. No thermostat, switch, or fluid device shall be so designed or located that its proper operation would be impaired by a longitudinal tilting of the incubator of as much as 15° from the horizontal, excepting on incubators that tilt the mattress holder only.
- g. A hygrometer shall be provided with any incubator that attempts to increase the absolute humidity near the infant above that which obtains in the room, the indications of which shall not differ from the relative humidity near the infant by more than 10 percent in absolute value.

Note 6. It is suggested that the more elaborate completely enclosed incubators should provide suitable means, such as an ice container or a cool-water container, appropriately designed and located, for controlling the temperature and the absolute humidity independently of each other and independently of room conditions. Such provision is especially necessary in completely enclosed incubators that are to be flooded with a relatively dry, controlled oxygen-rich atmosphere. In these incubators, on account of decreased ventilation, cooling may be needed to maintain the proper small but necessary heat dissipation from the infant. Cooling becomes increasingly important, with or without oxygen flooding, when the room temperature becomes as high as 80° F.

VI. OXYGEN-THERAPY EQUIPMENT

Note 7. Some models of incubators are designed to permit the introduction of a continuous or automatically controlled oxygenrich atmosphere. It is urged that all such arrangements and devices be safeguarded as far as possible against an excess of oxygen above the intended value.

- a. Any air-oxygen mixing valve shall be calibrated to show the resulting percentage of oxygen in the mixture in the incubator under operating conditions. Notice of the proper oxygen flow to be used with the calibration of the valve shall be clearly posted on the valve or the incubator. In any incubator that is to be flooded with an oxygen-rich atmosphere one or more suitable warning devices or indicators shall be arranged to show excess oxygen and failure of oxygen flow.
- b. Any incubator that is to be flooded with an oxygen-rich atmosphere shall be provided with a suitably located vent, through which test samples may be obtained.
- c. Any incubator that is to be flooded with an oxygen-rich atmosphere shall provide a suitable means for maintaining a satisfactory realitve humidity.

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Appendix 5

NEW YORK HOSPITAL

CHILDREN'S CLINIC-NURSE'S NOTES

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TODAY'S WEIGHT

HISTORY NO.

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Medical and Nursing Records

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NURSE'S NOTES-Continued

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Premature Infants

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Address			Mother	
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Activity				
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Medical and Nursing Records

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Scalp and Skull		
	Rectum	
Fontanelles		
	Extremities	×
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	Lower	
Ears		
Nose	Lymph. Nodes	
	Skin	
Mouth		
	Reflexes	
	Knee Jerks	Moro
	Ankle Jerks	Chvostek
Thorax	Ankle Clonus	Abdominals
Conformation	Biceps	Cremasterics
Respirations	Triceps	Babinski

PEDIATRIC NURSERY CHART-Continued

Premature Infants

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Medical and Nursing Records

	Impression;
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PEDIATRIC NURSERY CHART—Continued			
	DISCHARGE NOTE		
Discharged	19 on	days a	s after birth.
Weight Day of Discharge	Relation to Birth Weight		
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Premature Infants

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Medical and Nursing Records

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Medical and Nursing Records

Appendix 6

CATHETER FEEDING, OR GAVAGE 1

A catheter (No. 10 French for larger infants, No. 8 for smaller), about 14 inches in length, may be attached to the glass barrel of a small syringe. All food should be carefully measured and administered slowly with the minimum elevation required to obtain a free flow of milk. The infant should be upon its back on a flat surface, with its head in the median line and not elevated. The passage of the catheter into the esophagus is usually effected without difficulty. The poorly developed reflexes rarely cause severe retching. The catheter will not enter the larynx when being passed. It will either pass into the esophagus or turn upon itself, and in the latter case, the tip will come out of the mouth. No lubricant is required; the catheter should be passed dry.

The danger in catheter feeding comes at the time of withdrawal at the conclusion of feeding. At this time, if the catheter is not firmly compressed, or bent on itself, any milk remaining in the catheter will flow into the pharynx. As the infant usually gasps deeply at the time of withdrawal, any food in the pharynx may be aspirated into the larynx.

The distance to which the catheter is to be passed is of great importance when we consider that this procedure must be repeated at least six to eight times daily over a considerable period of time. It has been our rule to measure the distance from the bridge of the nose to the tip of the ensiform cartilage, which is usually from 10 to 15 cm. (full-term newborn infants average about 16 cm.). The catheter is marked at this point with a circle of indelible ink, a second circle is drawn 2 cm. above this point, and a third is made 4 cm. above the first.

The catheter is passed with the glass barrel empty in order to avoid spilling food into the pharynx. When the catheter is passed to the first mark, the tip reaches to about 1 cm. above the cardia. When passed to the second mark, the eye will have entered the stomach, and when the catheter is passed to the third mark, the tip will be well within the stomach. It becomes evident that each infant should have its individual catheter, as it is necessary for the nurse to have at all times a fairly definite idea as to the distance it has been passed, as well as to avoid the danger of cross infection. A nurse soon learns the distance that the catheter should be passed under the varying conditions. Most of the feedings are given with the top of the catheter in the lower end of the esophagus, to eliminate irritation of the gastric mucosa and stimulation of the reflex at the cardia.

¹Hess, Julius H.; and Lundeen, Evelyn C.: The Premature Infant: Its medical and nursing care. Phila.: Lippincott, [1941]. 309 pp. (p. 110)

If the stomach is dilated, it is usually clearly outlined through the thin abdominal wall. In the presence of gastric distention, raising the infant to a vertical position and allowing it to belch before passing the catheter will often avoid the necessity of passing the catheter into the stomach. If the gastric distention is not relieved by this procedure, the catheter is pressed to the second or third circle, as may be indicated, so that the top of the catheter enters the stomach. The empty glass barrel is then raised and the air allowed to escape in this manner before feeding is begun.

The milk is allowed to flow into the stomach, the glass barrel being raised from 6 to 8 inches above the level of the body. After the feeding, the catheter is firmly compressed or bent upon itself to avoid spilling milk into the pharynx during its removal.

Carefully elevating the child to a vertical position after feeding will allow the eruction of air and will frequently prevent cyanotic attacks. In elevating the child, flexion of the body must be avoided.

Too rapid feeding, with overdistention of the stomach, is more dangerous than too slow feeding. Usually, 2 or 3 minutes is all that is required. Turning the infant on its right side following the feeding reduces the emptying time. A single nurse can carry out catheter feeding once she becomes skilled.

The position of the infant should be changed at least once between feedings in order to avoid hypostatic pulmonary congestion.

The premature infant is not routinely belched, since all unnecessary handling is avoided. If the baby is regurgitating, and belching will aid in checking this, the child is elevated, not picked up. When the baby weighs $4\frac{1}{2}$ to 5 pounds, it can be picked up after feeding to allow it to belch.

Appendix 7

FLUIDS FOR PARENTERAL ADMINISTRATION

Fluid	Indication	Sc. == Iv. = Bm.=	Rout Subcutaned Intravenou =Bone mar	te ously sly row	Quanitity
Physiologic saline	Dehydration; mild al- kalosis or acidosis when renal function is	Sc	Iv	Bm	Iv. fluid at one time in vol. not greatly exceed- ing 10 cc. per lb. of
5 percent glucose in water or saline.	Ketosis; dehydration; inadequateoral intake.		Iv	Bm	than 10 cc. per min. Same vol. may be giv- en into bone marrow
Ringer type of solu- tion.	Dehydration; mild acid- osis.	Sc	Iv	Bm	7 at 12 the speed. Vol. and rate subcutan- eously limited by rate of absorption. If fluids are given cont., the daily vol. = approx. 2½ to 3 oz. per lb. of body weight for small infants.
Concentrate', glu- cose or sucrose (20 to 50 percent).	As a diuretic temporar- ily to reduce high in- tracranial pressure; hypoglycemic shock;		Iv	Bm	10-50 cc. at a time.
M/6 sodium lactate	Acidosis (CO ₂ above 20- 25 vol. percent).	Sc	Iv	Bm	Cc. molar lactate = wt. in kg. \times 0.3 \times CO ₂ deficit. Dilute with 5
Sodium bicarbonate.	Acidosis (CO: below 20- 25 vol. percent).		Iv	Bm	Cc. 5 percent solution = $20 \text{ (wt. in kg. } \times 0.026$ $\times CO_{2} \text{ deficit}$
Amino acids	Inadequate oral intake of protein; surgical conditions; diarrhea, etc. nenbrosis	Sc	Iv	Bm	
Plasma	Shock; burns; hypopro- teinemia; edema; to avoid hypoprotein- emia when entire fluid intake is by parenteral routes	·	Iv	Bm	May be used in normal strength or if dried plasma is used, it may be concentrated 3 to 4 times.
Whole blood	Anemia; to supply anti- body and comple- ment; to supply car- bonic anhydrase in premature infants.		Iv	Bm	Always type and cross match. 15 cc. per kg. of body weight raises blood count by approx. 1 million.

¹ Mitchell-Nelson Textbook of Pediatrics. 4th ed. rev. Phila.: Saunders, [1947]. 1352 pp. (p. 177) 388

Appendix 8 SUCGESTED TABULATION FORM

- Hospital

Report period: Initial date:

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	month	day	year		плони	uay yea			
	Live-bo	rn prematur	e infants	Deaths (of live-born p infants	remature	Fatality rat 100 live-bo	e (number o orn prematu	f deaths per re infants)
Birth weight	Total (1)	White (2)	Nonwhite (3)	Total (4)	White (5)	Nonwhite (6)	Total (7)	White (8)	Nonwhite (9)
				BORN I	N THIS H	OSPITAL			
Total, 2,500 gm. or less	Number	Number	Number	Number	Number	Number	Percent	Percent	Percent
1,000 gm. or less								ŕ	
				ADMIT	ED AFTE	R BIRTH			
Fotal, 2,500 gm. or less									
88 1,000 gm. or less									

4ppendix 9

CONVERSION TABLES

Conversion of pounds and ounces to grams

Ounces	1 lb.	2 lb.	3 lb.	4 lb.	5 lb.	6 lb.	7 lb.	8 lb.
0	Gm. 454	Gm. 907	Gm. 1, 361	Gm. 1.814	Gm. 2, 268	Gm. 2.722	Gm. 3.175	Gm. 3,629
1	482 510	936 964	1, 389 1, 418	1, 843 1, 871	2, 296 2, 325	2, 750 2, 778	3, 204 3, 232	3, 657 3, 686
3 4	539 567 595	992 1,021 1,049	1, 446 1, 474 1 503	1, 899 1, 928 1, 956	2, 353 2, 381 2, 410	2, 807 2, 835 2, 863	3, 260 3, 289 3, 317	3, 714 3, 742 3, 771
6 7	624 652	1,077 1,106	1, 531 1, 559	1, 985 2, 013	2, 438 2, 466	2, 892 2, 920	3, 345 3, 374	3, 799 3, 827
89	680 709	1, 134 1, 162	1, 588 1, 616	2,041 2,070	2, 495 2, 523	2, 948 2, 977	3, 402 3, 430	3, 856 3, 884
10 11 12	737 765 794	1, 191 1, 219 1, 247	1, 644 1, 673	2,098 2,126 2,155	2, 552 2, 580 2, 608	3,005 3,033 3,062	3, 459 3, 487 3, 515	3, 912 3, 941 3 969
13 14	822 851	1, 276 1, 304	1, 729 1, 758	2, 183 2, 211	2, 637 2, 665	3, 090 3, 119	3, 544 3, 572	3, 997 4, 026
15	879	1, 332	1, 786	2, 240	2, 693	3, 147	3, 600	4,054

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 grams. To convert into pounds and ounces a weight in grams not shown in the table multiply the number of grams by .002205=2.77830, or 2.78 lb., or 2 lb. $12\frac{1}{2}$ oz.

Conversion of inches to centimeters

Inches	Centimeters	Inches	Centimeters	Inches	Centimeters
$ \begin{array}{c} 10\\ 10\frac{1}{2}\\ 11\\ 11\frac{1}{2}\\ 12\frac{1}{2}\\ 13\\ 13\frac{1}{2}\\ 14\\ 14\frac{1}{4}\\ 14\frac{14}\\ 14\frac{14}\\ 14$	25. 40 26. 67 27. 94 29. 21 30. 48 31. 75 33. 02 34. 29 35. 56 36. 83	15 151/2 16 161/2 17 171/2 18 181/2 19 191/4	38. 10 39. 37 40. 64 41. 91 43. 18 44. 45 45. 72 46. 99 48. 26 49. 53	20 201/2 21 211/2 22 221/2 23 231/2 23 231/2 24	50. 80 52. 07 53. 34 54. 61 55. 88 57. 15 58. 42 59. 69 60. 96

The table shows the equivalent of inches in centimeters, by half-inch intervals from 10 to 24 inches. Since 1 inch is equal to 2.54 centimeters, 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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Auxiliary Care

(Two case illustrations)

Auxiliary care is service given to the family during the hours of employment of the mother. In such a situation the primary responsibility for the maintenance of the home and the care of the children remains with the mother. The homemaker works under her direction with such guidance from the social agency as is required by the mother or the homemaker.

FAMILY NAME: Malone. Father: Barry, 28 years. Mother: Rose Marie, 26 years. Children: Robert, 5 years. Mary Anne, 3 years. Barry, 1 year.

Mrs. Malone was referred to homemaker service by the Army Emergency Relief Agency when she appealed to them for advice and assistance. Mr. Malone was in the Army and his allotment had not yet come through. Arrangements had been made with Mrs. Malone's sister to care for the children while Mrs. Malone trained for a defense job. She completed her training and had been on a defense job not far from her home for the past 2 weeks. She was earning \$28 weekly with an opportunity for immediate advancement. Everything was working satisfactorily when her sister became ill and entered the hospital for an emergency appendectomy. Mrs. Malone had to remain at home to care for the children. She applied to day nurseries and was told that there were waiting lists. In addition, no nursery could accommodate the baby.

Mrs. Malone had to work to pay her family expenses. She had been reporting to the job in order not to lose her rating. An immediate appointment was made for Mrs. Malone to discuss homemaker service with the case worker. Mrs. Malone's hours of work, as well as plans for the care of her three children, were talked over carefully. She revealed herself to be keenly aware of the differing personalities of the children. Robert was very mischievous and behaved very badly if told abruptly not to do a thing. Mary Anne was apt to follow Robert in his mischief making. They loved to be read to and enjoyed acting out the stories. Barry had been quite ill and had a special medicine and routine. The worker felt that Mrs. Malone had been thoughtful about the children's care and that her husband had entered service after they both agreed that he should and had arranged for the care of the home and children.

The hours for the homemaker were settled, and it was agreed service would start the following morning in time for Mrs. Malone to report to her job. Mrs. Malone was told that the homemaker had been a kindergarten teacher who had a baby's nursing certificate. The homemaker was called by telephone while Mrs. Malone was at the office and reported to the Malone home as scheduled. The worker called upon her that day. Service was given in the home for a 4-week period during the hours the mother worked. At the end of that time, Mrs. Malone's sister returned to the home and both Mrs. Malone and she agreed they could manage.

FAMILY NAME: Plant. Father:

Mother : Children : Richard, 36 years. Jane, 32 years. Richard, 8 years. Lawrence, 6 years. Benjamin, 4 years.

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Mrs. Plant worked on a night shift in a defense industry as a specialized shipper. Mr. Plant worked during the day as a truck driver for the same firm. The two older children attended school and Benjamin was attending a day nursery. Benjamin had had a heavy cold and could not be admitted to the group until the cold was cleared.

Mr. and Mrs. Plant had made very careful plans for the children. The mother got home from work in time to get the children up and ready for school. Then she rested and did her share of the housework and was ready to spend the evening with her children and husband. Since Benjamin had been at home ill, the mother had been unable to get enough rest to do justice to her job or to the child. The doctor and nursery visitor felt that she was becoming overtired and that the child's condition was not clearing as rapidly as it should.

A case worker of the homemaker service called upon Mrs. Plant and explained the service. Due consideration was given to the family's ability to contribute to the cost of the homemaker. A homemaker who had worked closely with nursery schools in other situations was assigned to the family, and her work was confined to the care of Benjamin during the mother's rest hours. The service covered a 12-day period and was paid for in full by the family.

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