NEONATOLOGY

Pathophysiology and Management of the Newborn

Fifth Edition

Edited by

GORDON B. AVERY, M.D., PH.D.
Emeritus Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences; and
Scholar in Residence
Children's Research Institute
Children's National Medical Center
Washington, D.C.

MARY ANN FLETCHER, M.D.
Clinical Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Washington, D.C.; and
Staff Neonatologist and Director
Newborn Follow-Up Program
Shady Grove Adventist Hospital
Rockville, Maryland

MHAIRI G. MACDONALD, M.B.CH.B., F.R.C.P.(E), D.C.H.
Clinical Professor of Pediatrics
The George Washington University School of Medicine and Health Sciences
Washington, D.C.; and
Director, Neonatology Services
Loudoun Hospital Center
Leesburg, Virginia

WITH 111 CONTRIBUTORS

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

CHAPTER 59

Developmental Outcome

Forrest C. Bennett

More than 250,000 low-birth-weight infants (LBW; ≤2,500 g) are born each year in the United States, constituting approximately 7% of all live births. Of these infants, approximately 50,000 annually are of very low birth weight (VLBW; ≤1,500 g), constituting approximately 1.5% of all births. Because the estimated LBW incidence has remained relatively stable over the past 40 years (Fig. 59–1), contemporary reductions in neonatal mortality are steadily increasing the prevalence of biologically vulnerable infants and children in the overall population (1).

Although much medical, legal, ethical, and economic debate continues to occur over the effects of neonatal intensive care on the long-term developmental status of LBW survivors, most investigators are in agreement that the single clearest outcome of this technically enhanced care has been a dramatic and continuing reduction in neonatal mortality since the early 1960s, particularly for VLBW infants since the mid-1970s (see Fig. 59–1) (2,3). With current standards of practice in the neonatal intensive care unit (NICU), many more LBW, premature infants are surviving to be discharged home after extended hospitalizations than was the case even 5 to 10 years ago. The major factors responsible for this increased survival include the technical ability to provide assisted mechanical ventilation to the smallest of LBW infants; the regionalization of perinatal–neonatal care, with greater numbers of maternal transports to and infants born in tertiary centers; and the widespread use of exogenous surfactant.

Remarkable improvements in the birth-weight–specific mortality rates accounted for 90% of the overall decline in neonatal mortality between 1960 and 1980 (4). During these two decades, decreases in the mortality rates of infants weighing between 1,500 and 2,500 g contributed more than any other weight group because of both greater proportional decreases and higher absolute declines in mortality; however, there has been steady and statistically significant reduction in mortality rates among VLBW infants throughout the last 15 to 20 years. Mortality for infants with birth weights of 1,001 to 1,500 g has fallen from more than 50% in 1961 to less than 10% today. Moreover, the most substantial improvement of the 1980s over the 1970s in neonatal mortality rates was in the 751 to 1,000 g birth weight group, where today's infants have greater than an 80% chance of surviving if they are admitted to an NICU (5). Finally, in the 1990s, 40% to more than 60% survival for infants between 500 and 750 g birth weight is being accomplished (6–8). The intact survival of a 380-g infant has been described (9).

Although survival continues to increase in all LBW categories, the greatest impact of neonatal intensive care technology clearly has been on the smallest, sickest, and

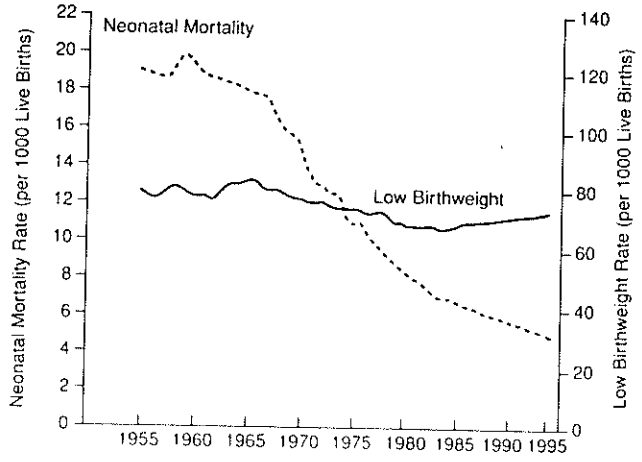

FIG. 59–1. United States annual rates of neonatal mortality and low-birth-weight births from 1955 to 1995. (Adapted from Lee KS, Paneth N, Gartner LM, et al. Neonatal mortality: an analysis of the recent improvement in the United States. *Am J Public Health* 1980;70:15, with permission.)

F. C. Bennett: Department of Pediatrics, University of Washington, Seattle, Washington

most medically fragile infants. The success in achieving these improved survival rates for LBW, premature infants raises obvious concerns about the subsequent development of such vulnerable infants. It mandates an organized neurodevelopmental follow-up approach to carefully and continuously monitor the quality of survival of the NICU graduate.

ORGANIZATION OF A HIGH-RISK INFANT FOLLOW-UP PROGRAM

Objectives

There are a number of compelling reasons for conducting longitudinal neurodevelopmental surveillance of survivors of neonatal intensive care. There also are practical problems encountered in providing comprehensive follow-up services. Individual follow-up programs must clearly define their own goals and objectives and then organize their roles and activities accordingly. A community hospital's follow-up efforts likely will be determined by a different set of expectations than those of a university-affiliated tertiary care center. Furthermore, ideal follow-up care in the United States frequently is constrained by limited resources. In general, follow-up programs are designed to meet one or more of the following objectives.

Quality Control

Regular, periodic follow-up of a large proportion of survivors can provide one type of audit of an individual NICU's performance. Because intensive care nurseries differ in such critical management areas as neonatal resuscitation, modes of assisted ventilation, treatment of ventriculomegaly, and use of parenteral nutrition, and also in such neonatal outcomes as mortality and prevalence of medical complications [e.g., bronchopulmonary dysplasia (BPD), intracranial hemorrhage], units may wish to compare their neurodevelopmental morbidity with the contemporary experience of similar nurseries (10). They also may wish to monitor their major disabling morbidities from year to year to detect any significant differences that might accompany further reductions in mortality or the introduction of new intensive care procedures or treatments. It must be recognized that follow-up at 1 or 2 years of age, although providing much useful information about the prevalence of major neurosensory impairment among survivors, is of insufficient duration to identify changes over time in more subtle aspects of brain function such as learning and behavior.

Developmental Services

Neurodevelopmental follow-up can provide important ongoing subspecialty care to at-risk children and families. Follow-up clinic personnel with a multidisciplinary approach will likely have the most experience and expertise in a given community concerning the unique developmental patterns of LBW, premature infants. In general, the follow-up program will complement and serve as secondary or tertiary developmental consultants to the primary health care providers. The program will encourage and facilitate the establishment of a community-based medical home (e.g., private practitioner, public health clinic) for every medically complex survivor. Experience with biologically and environmentally vulnerable indigent populations, however, suggests that actual provision of primary health care, in addition to evaluation and case management services, may be necessary in some situations to prevent attrition and maintain contact with those children and families at greatest long-term risk (11). Although the appropriate approach to this issue of role definition is likely to vary with different populations and access to medical care in different settings, it obviously is of fundamental importance to the organization of follow-up clinics and also to the maintenance of mutual trust relationships with the primary care community.

The specific objectives of follow-up neurodevelopmental assessment activities may be grouped conveniently as follows: to provide cautious reassurance to anxious parents; to ensure early identification and intervention for persistent developmental abnormalities; and to recognize the natural history of transient developmental abnormalities and thereby avoid unnecessary, costly interventions. Maintaining an appropriate balance of diagnostic and reassurance functions is one of the greatest challenges for the contemporary high-risk follow-up program.

Developmental Training

The follow-up clinic provides a marvelous setting for interdisciplinary developmental training. It is a clinical laboratory for the observation of the gradual recovery and normalization over time of most at-risk infants and, in other cases, the gradual evolution of a wide variety of permanent neurodevelopmental dysfunctions. Thus, the at-risk population offers a longitudinal training experience that spans the normal–abnormal development continuum. In many pediatric training programs, the follow-up clinic is the sole opportunity for pediatric residents to observe the outcomes of their own intensive care efforts. It would seem virtually impossible for physicians to be informed adequately about the ethical debates and dilemmas surrounding neonatal intensive care without a first-hand follow-up experience. Likewise, other child development professionals (e.g., psychologists, physical therapists, communication disorders specialists) can use the follow-up clinic profitably as a diverse training base, particularly to broaden the range of normative development for their students. Obviously, these training objectives will apply primarily to university-affiliated tertiary care centers, with their numerous and varied trainee availability.

Outcome Research

The university-affiliated follow-up program should be engaged actively in clinical research that contributes to the understanding of the neurodevelopmental and neurobehavioral outcomes of children who experienced neonatal intensive care. These studies may take the form of either descriptive observational reports or clinical trials of specific perinatal–neonatal interventions. For example, the University of Washington's High Risk Infant follow-up Program has published studies describing the outcome of infants weighing less than 800 g at birth (12–14) as well as studies evaluating the utility of procedures such as electronic fetal monitoring of premature labor and delivery (15) and treatments such as high-frequency mechanical ventilation (16). Although tremendous variability exists in the target populations, methodologies, and general scientific quality of the accumulated high-risk follow-up research, a growing consensus of valid outcome observations gradually has emerged over the last 30 years, and informative summary conclusions can be synthesized. Even though the ideal, population-based, non–risk-controlled, longitudinal to school age study rarely is accomplished for a variety of practical reasons (e.g., cost, subject mobility, investigator discontinuity), individual follow-up investigations, carefully performed albeit with a limited scope, continue to modify and refine overall knowledge and, in some cases, challenge assumptions.

This is not to say that broad, well-funded, collaborative follow-up efforts should not be pursued vigorously on both regional and national, and even international, levels. A recognized need for uniform population descriptions, standardized assessment protocols, common disability definitions, and adequate numbers of pooled subjects still exists. Threats to the interpretability and generalizability of small, local studies include population demographic bias, neonatal treatment differences, attrition of highest-risk (i.e., doubly vulnerable) subjects, and cross-sectional data analysis combining multiple age endpoints. A great deal has been learned about the short- and long-term prognoses of NICU survivors from hundreds of independent follow-up studies, but much more has yet to be clarified by enhanced research approaches (17).

Personnel

The size and complexity of the neurodevelopmental follow-up team depend on the scope of the program and the size of the patient population. For example, a level II or III community hospital with primarily developmental service objectives will likely employ a smaller team, follow for a shorter period of time, and administer fewer standardized measures than a university-affiliated tertiary care center with training and research responsibilities. In either case, certain key tasks must be accomplished. Probably the most critical role in terms of maximizing follow-up compliance and minimizing attrition is that of the follow-up coordinator, usually a program nurse. This person is the liaison between the NICU and the follow-up clinic. The nurse coordinator can identify and meet eligible infants and families before they leave the nursery, participate in the discharge conference and transition plans, and, in some cases, make preliminary contact with the family by means of a home visit before the initial follow-up evaluation. This liaison function is particularly important in those programs that conduct high-risk follow-up at a separate site away from the intensive care nursery and in which none of the follow-up personnel is actively involved in the NICU.

Overall program direction is typically provided by a physician or psychologist. This person ultimately is responsible both for meeting the broad programmatic objectives and also for day-to-day operations. The director of a university-affiliated follow-up program frequently must balance competing service, training, and research obligations while eclectically maintaining sufficient funding sources to ensure long-term program viability. The director certainly should be knowledgeable in terms of current follow-up literature and contemporary models of program structure and function.

Other follow-up roles of the interdisciplinary team include the following:

Medical–neurologic assessment. This may be provided by a neonatologist, developmental pediatrician, or child neurologist. In some programs a pediatric nurse practitioner or the nurse coordinator may provide health, nutritional, and behavioral guidance pertaining especially to such issues as feeding, sleeping, temperament, and discipline.

Developmental–intellectual–academic achievement assessment. This often will be performed by a physical therapist during infancy and by a clinical psychologist or psychometrist thereafter. Some tertiary centers may use a neuropsychologist at school age. In some programs, an early childhood educator or infant developmental specialist participates in early assessments.

Neuromotor assessment. This usually will be done by a physical therapist during the first years of life when gross motor concerns are paramount, and then by an occupational therapist during the preschool and school years when fine motor concerns predominate.

Language–speech assessment. In many follow-up programs, this responsibility is assumed by the psychologist. Some programs have the necessary personnel and funding resources to use a communication disorders specialist on a regular basis.

Family assessment. The increasingly important task of evaluating and monitoring the home parenting environment may be performed by a social worker, a clinical nurse specialist, or both. As the number of dysfunctional families in the NICU setting steadily increases because

of such prevalent influences as poverty, single parenthood, and prenatal substance abuse, so does the requirement of follow-up programs increase for qualified psychosocial personnel.

Hearing assessment. The adequate ability to assess hearing at any age by a clinical audiologist is imperative for tertiary follow-up programs. Both electrophysiologic and behavioral audiometric procedures should be available.

Visual assessment. A pediatric ophthalmologist should be readily accessible by consultation to the follow-up program, particularly for extremely low-birth-weight (ELBW; ≤1,000 g birth weight) infants.

Patient Selection

Once again, the goals, objectives, personnel, and resources of an individual follow-up program will combine to determine the proportion and nature of at-risk survivors that can be served. Since it usually is impossible for a program to follow all infants receiving neonatal intensive care, somewhat arbitrary risk criteria generally are established to provide broad follow-up guidelines (18). In light of the variation and imperfection of assigned risk factors in accurately predicting neurodevelopmental outcome, a follow-up program is wise to adopt a flexible, rather than rigid, approach to the issue of eligibility. In general, a follow-up program will target the smallest and sickest NICU graduates to maximize the likely necessity of its services. Different levels of follow-up priority (e.g., high, medium, low) frequently are used to structure the selection and longitudinal monitoring process. University-affiliated follow-up programs conducting specific clinical research will tailor patient selection according to study requirements.

Common risk criteria for follow-up include the following factors:

- VLBW. In smaller programs with limited personnel and resources, the birth weight criterion may, by necessity, be arbitrarily lowered to 1,250, 1,200, or even 1,000 g. This category also generally will incorporate those infants of 32 weeks of gestational age or younger.
- Small for gestational age (SGA). Most programs strive to include infants whose weight or head circumference at birth was more than two standard deviations below the mean for gestational age.
- BPD. Programs will vary on the required duration of mechanical ventilation and oxygen administration.
- Neuroimaging abnormalities. This criterion typically will include such findings as severe intracranial hemorrhage (e.g., large intraventricular hemorrhage, intraparenchymal hemorrhage), severe ventriculomegaly, or extensive cystic periventricular leukomalacia.
- Prolonged seizures or other abnormal neurologic behavior. This would include those infants who continue to demonstrate an atypical neurologic examination at the time of nursery discharge.
- Central nervous system infection. The targeted infection may have occurred during the intrauterine, intrapartum, or neonatal time period.
- Miscellaneous perinatal–neonatal events of potential neurodevelopmental significance. Most programs will prioritize infants who have experienced to a severe degree such complications as asphyxia, hyperbilirubinemia, hypoglycemia, or polycythemia. Specific threshold determinations will vary from program to program. Table 59–1 quantifies the major neurodevelopmental risk associated with many of these follow-up inclusion criteria.

Many states use or are developing some type of comprehensive high-risk tracking or screening system to monitor the growth and development of biologically vulnerable infants (19). In some states (e.g., Iowa, North Carolina, Washington), this broadly based tracking system serves as an initial screen to identify those infants and toddlers who merit complete, tertiary developmental assessment. This coordinated approach to follow-up offers the advantages of tracking many more at-risk infants and families while also increasing the efficiency and appropriate use of the formal follow-up clinic.

Clinic Schedule

The schedule of evaluations conducted by the University of Washington's High Risk Infant Follow-up Program is

TABLE 59–1. *Risk factors for major neurologic and cognitive sequelae in surviving infants requiring neonatal intensive care*

Birth weight (g)	Category	Risk factor (%)
>2,500	All admissions	<5
	Respiratory distress syndrome	5
	Postasphyxia seizure	30–50
	Meningitis	30–50
1,501–2,500	All admissions	10
	Small for gestation age	<10
	Respiratory distress syndrome	<10
	Bronchopulmonary dysplasia	20–30
	Postasphyxia seizure	30–50
	Meningitis	30–50
≤1,500	All admissions	10–30
	Appropriate for gestational age, nonventilated	10–15
	Appropriate for gestational age, ventilated	30–40
	small for gestational age	30–50
	Seizures, decerebrate posture	75–80
≤1,000	All admissions	10–40

Adapted from Fitzhardinge PM. Follow-up studies of the high-risk newborn. In: Avery Gb, ed. *Neonatology: pathophysiology and management of the newborn,* 2nd ed. Philadelphia: JB Lippincott, 1981:353.

utlined in Table 59–2. This plan is illustrated as an exam-le of a follow-up program with combined clinical service, aining, and research objectives. Smaller hospital-based rograms without training or research requirements often ill be able to meet their clinical needs with different for-ats, shorter duration of follow-up, and fewer standard-ed assessments. Basic monitoring concepts applicable to ll follow-up programs, however, include special attention neuromotor development the first year, language and gnitive development the second and third years, school adiness skills between 4 and 5 years of age, and acade-ic achievement during the early school years. In addition, tention to family function ideally should be an integral rt of each clinic visit. With this developmental sequence evaluations, timely identification of delays and dysfunc-ns as well as appropriate referral to community-based tervention services are optimized (20).

A frequent topic of debate concerns the calculation of sessment age for premature infants (21). Whereas most llow-up programs plan their clinic visit schedule and ore their evaluation measures on the basis of fully cor-ted age (i.e., chronologic age minus the number of eks premature), a number of others continue to use adjusted chronologic age or even, in a few cases, one-lf correction (i.e., chronologic age minus one-half the mber of weeks premature). The reluctance to use full stational age correction stems from a concern over the potential artificial inflation of developmental test scores and coincident underuse of early intervention services during the first several years of life. Although these are valid clinical concerns to consider when providing parental feedback and making referral decisions, the weight of the evidence in terms of the neuromaturation of premature infants favors the practice of gestational age correction, at least to 3 years of age, when monitoring the growth and development of NICU survivors.

Regardless of the scheduling mode used, all follow-up personnel must appreciate the imprecisions and variabilities of early developmental assessment. Low-birth-weight, premature infants may demonstrate improving developmental performance during the first years of life as they recover from perinatal–neonatal insults and chronic health impairments (e.g., BPD, necrotizing enterocolitis). Conversely, they also may demonstrate additional developmental dysfunction over time as more subtle disabilities become increasingly apparent and testable. In light of these patterns of development, health and developmental professionals who work with premature infants and their families must be aware of the hazards implicit in the high-risk concept. Parents may permanently regard their child as vulnerable, once so labeled, and contribute to a self-fulfilling prophecy. There can be an overzealous tendency in well-intended follow-up programs to presume the presence of abnormality rather than normality, despite the evidence of more optimistic outcome data to the contrary. In fact, most high-risk infants do not develop the conditions for which they are at increased statistical risk, and there frequently is a poor correlation between the severity of the neonatal course and specific neurodevelopmental outcomes for individual premature infants. There is a need for monitoring of this population with a keen awareness of, but not an expectation of, adverse sequelae. Documented developmental dysfunction certainly should not be ignored, but an initial follow-up posture of cautious optimism is appropriate in most cases.

TABLE 59–2. *High-risk infant follow-up clinic schedule*

Corrected age	Test
no	BSID[a]
	MAI
	Physical and Neurologic Examination
no[b]	BSID
	MAI
	Audiologic Evaluation by Visual Reinforcement Audiometry
	Physical and Neurologic Examination
mo	BSID
	Physical and Neurologic Examination
mo	BSID
	Physical and Neurologic Examination
mo	Stanford–Binet Intelligence Scale
	Peabody Picture Vocabulary Test
	Expressive Language Sample
	Physical and Neurologic Examination
years	Wechsler Preschool and Primary Scale of Intelligence
	Peabody Developmental Motor Scales
	Physical and Neurologic Examination
d 8 years	Wechsler Intelligence Scale for Children
	Peabody Individual Achievement Test
	Physical and Neurologic Examination

BSID, Bayley Scales of Infant Development; MAI, Movement Assessment of Infants.
Scheduled selectively for those infants with possible neuromotor abnormalities at 4 months of age.

NEURODEVELOPMENTAL OUTCOME OF LOW-BIRTH-WEIGHT PREMATURE INFANTS

Despite contemporary reductions in LBW morbidity compared to disability rates before the introduction of neonatal intensive care, permanent neurodevelopmental problems are seen in many survivors. Such problems include major neurosensory impairments, cognitive and language delays, specific neuromotor deficits, neurobehavioral and socioemotional abnormalities, and school dysfunction (22).

Major Neurosensory Impairments

The major neurosensory impairments associated with prematurity are cerebral palsy, particularly of the

spastic diplegia type; mental retardation [i.e., intelligence quotient (IQ) more than two standard deviations below the standardized test mean]; sensorineural hearing loss; and visual impairment, primarily the consequences of retinopathy of prematurity (ROP) (23). These major developmental disabilities may occur together in the same child and occasionally are complicated by progressive hydrocephalus or a chronic seizure disorder. They usually are clinically apparent by 2 years of age and vary in severity from mild to profound. Children with one or more of these major impairments generally require special educational programming and individual therapeutic intervention throughout childhood. These conditions occur two to five times more frequently in LBW compared to full-birth-weight (FBW) infants. As a group, their prevalence increases with decreasing birth weight and gestational age; the disability rate in boys consistently exceeds that in girls (24). Table 59–3 provides combined prevalence estimates and ranges by birth weight group for these chronic neurosensory impairments. The actual numbers represent a synthesis from reporting tertiary care centers in the United States, Canada, Australia, and Western Europe.

Such major morbidity statistics may be viewed either positively or negatively, or both. On the one hand, the occurrence of these major sequelae is far less than initially predicted at the beginning of the NICU era, and many more nondisabled than disabled survivors (approximately 8:1) are being added to the population (25). Conversely, epidemiologic investigations appear to document that reductions in LBW major morbidity have not paralleled or kept pace with reductions in LBW mortality and that the major impairment rate has changed little over the past 20 to 25 years. Actual increases in both the incidence and prevalence of major disabilities among the smallest and sickest survivors have been reported by some (26,27). Others, however, have reported a stable major morbidity rate for infants weighing less than 800 g at birth (Table 59–4), a subgroup whose survival has dramatically increased during this time period (12–14). This encouraging observation that the overall incidence of serious neurodevelopmental deficits is remaining stable while survival continues to increase has been repeatedly corroborated even for those ELBW infants who weighed less than 750 g at birth (8,28–30).

TABLE 59–3. *Low-birth-weight infants who survive with one or more major impairments*

Birth weight (g)	Percent with major impairments (range)
1,501–2,500	8 (5–20)
1,001–1,500	15 (5–30)
≤1,000	25 (8–40)

TABLE 59–4. *Prevalence of major impairments in survivors weighing less than 800 g at birth at the University of Washington*

	Major impairment (%)
1986–1990	17/78 (22)
1983–1985	8/38 (21)
1977–1980	3/16 (19)

From LaPine TR, Jackson JC, Bennett FC. Outcome of infants weighing less than 800 grams at birth: 15 years' experience. *Pediatrics* 1995;96:479.

Cerebral Palsy

Cerebral palsy, of varying types and severities, remains the most prevalent major developmental disability encountered in premature infants; the prevalence in VLBW infants varies between 6% and 10%, and approximately 40% of all children with cerebral palsy were born prematurely (i.e., <37 weeks of gestation) (31). Although both spastic (i.e., pyramidal) and athetoid (i.e., extrapyramidal) types of cerebral palsy may be encountered in NICU graduates, the spastic cerebral palsy syndromes (i.e., diplegia, hemiplegia, and quadriplegia) are the neuromuscular disorders most commonly seen in LBW infants. One specific type, spastic diplegia, in which the legs are much more affected than arms, is so strongly associated with prematurity (i.e., at least twothirds of all children with this disorder are born before 37 weeks of gestation) that for over a century it has been referred to as "the disease of immaturity" (31a). Figure 59–2 illustrates the relationship between spastic diplegia and gestational age. Most cases occur in a window of vulnerability in infants born between 28 and 34 weeks of gestation.

Despite the long consistency of the spastic diplegia–prematurity association, the exact etiologic factors involved often have been elusive and difficult to identify precisely prospectively (32). Neither the severity of perinatal–neonatal illness nor the presence or the severity of intracranial

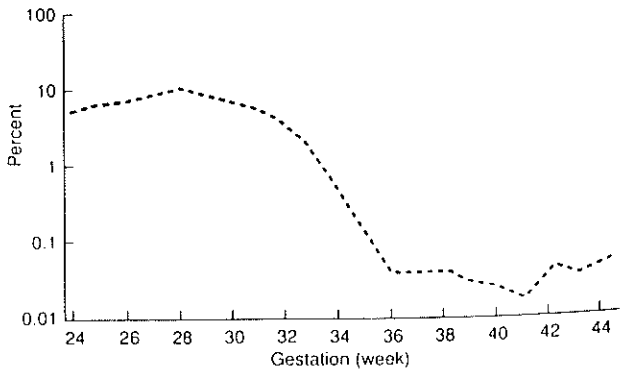

FIG. 59–2. Occurrence of spastic diplegia as related to gestational age.

hemorrhage reliably predicts spastic diplegia. Data derived primarily from studies correlating ultrasonographic, neuropathologic, and clinical information led to the conclusion that spastic diplegia is the clinical expression of periventricular leukomalacia and its variants (33). Periventricular leukomalacia appears to be caused, in large part, by hypoxic–ischemic injury to the periventricular white matter. The demonstration on serial cranial ultrasounds of initial extensive periventricular echodensities followed in days to weeks by large, bilateral cyst formation (i.e., periventricular white matter infarction) is highly predictive (80% to 85%) of permanent cerebral palsy, especially the spastic diplegia type (34,35). Many cases of symmetric cystic periventricular leukomalacia occur in infants with relatively benign clinical courses and are detected only by routine ultrasound screening. Premature infants born to mothers with prolonged rupture of membranes and/or chorioamnionitis seem to be at an increased risk (36). Several investigators have implicated prenatal factors (e.g., intrauterine growth retardation) in the etiology of some cases of spastic diplegia. Hagberg has postulated that the complex interaction of prenatal abnormalities (i.e., "fetal deprivation of supply") with perinatal difficulties in the birth process and the adjustment to the extrauterine environment may constitute a common pathogenetic mechanism of spastic diplegia (37). Accordingly, the etiology of spastic diplegia frequently is multifactorial, and all LBW infants merit close neuromotor monitoring during the first 2 years of life, regardless of the severity of their nursery course.

In contrast, development of the more severe spastic quadriplegia type of cerebral palsy, in which all four extremities are equally affected, often can be predicted better in NICU graduates on the basis of specific perinatal or neonatal events, including asphyxia, marked bilateral intraventricular hemorrhage with ventriculomegaly, prolonged neonatal seizures, and central nervous system infection. Although most premature children with spastic diplegia have average or near-average mental abilities, children with spastic quadriplegia are far more likely also to have serious cognitive impairments. Spastic hemiplegia, in which only one side is affected, with the arm usually more than the leg, often is heralded by the ultrasonographic appearance of a unilateral, periventricular hemorrhagic infarction with subsequent cystic transformation that occurs in association with and presumably as a result of substantial asymmetric intraventricular hemorrhage (33).

Cerebral palsy typically presents over time in a developmental manner. Thus, very early neurologic signs and symptoms may prove to be transient in nature and not indicative of eventual cerebral palsy. Conversely, infants who initially appear asymptomatic with a relatively normal neurologic examination at the time of nursery discharge and even for several months thereafter, particularly in the cases of spastic diplegia and spastic hemiplegia, only to manifest clearly evident cerebral palsy by 1 year of age. Premature infants with evolving cerebral palsy reveal increasing neuromotor abnormalities of muscle tone, movement, posture, and reflex activity, particularly between 6 and 18 months of corrected age, in combination with increasingly delayed motor milestones.

Mental Retardation

Mental retardation, as defined by a standardized intelligence or developmental quotient consistently more than two standard deviations below the test mean for corrected age, often occurs in conjunction with one or more of the other major handicaps, especially cerebral palsy. In fact, severe mental retardation and severe cerebral palsy share associated perinatal–neonatal risk factors. Evidence suggests some increase in the prevalence of severely multihandicapped children after increased VLBW survival (27). Mental retardation occurs in 4% to 5% of VLBW infants followed longitudinally to school age. Isolated mental retardation, without cerebral palsy, is a reported consequence of severe BPD, particularly in cases of greatly prolonged duration of mechanical ventilation and oxygen administration (38,39).

Hearing Impairment

Neonatal intensive care unit graduates are at increased risk for both sensorineural and conductive hearing loss. Although the risk of sensorineural loss sufficient to require hearing aids, special education, and nonvocal communication strategies (60 to 100 dB) usually is estimated to be 2% to 3% for VLBW infants, some investigators have reported prevalence estimates between 5% and 9% coincident with the increased survival of more vulnerable infants (40). Exposure to ototoxic drugs, infections, hypoxia/ischemia, and hyperbilirubinemia are among the interacting and cumulative factors contributing to the risk of sensorineural loss. The duration and extent of hyperbilirubinemia in VLBW infants has been examined carefully. DeVries and colleagues found bilirubin levels in excess of 14 mg/dL to be associated with a high risk of deafness in VLBW infants but not in healthy premature infants with a birth weight greater than 1,500 g (41). Others also have emphasized the potential ototoxicity of hyperbilirubinemia in VLBW infants in combination with hypoxia, acidosis, and prolonged administration of multiple ototoxic medications such as the aminoglycoside antibiotics and furosemide. These investigators conclude that the additive effects of protracted illness plus its associated treatments, independent of specific diagnostic categories, constitute important risk factors for permanent hearing loss in this population (42).

There is ample evidence that infants of all birth weights who sustain severe persistent pulmonary hypertension of

the newborn comprise a particularly high-risk subgroup for sensorineural hearing loss, with prevalence estimates ranging from 20% to 40% (43). In some cases, the loss is progressive during the first 3 years of life. The exact mechanism of insult remains unclear in this population of infants who typically experience prolonged hypoxia, severe acute and chronic lung disease, and multiple aggressive interventions. Another concern has been the potential deleterious effect of prolonged incubator noise on hearing function. Abramovich and associates found no evidence for this hypothesis in VLBW infants (44). Many of the risk factors associated with hearing impairment also are associated with cerebral palsy, and these two disabilities often occur together in the same child.

Mild and moderate (25 to 59 dB) sensorineural hearing losses, sufficient to contribute to delayed language development but compatible with oral communication, also occur with increased frequency (6% to 8%) in LBW infants. Previously unrecognized unilateral sensorineural hearing losses, with adverse language and learning consequences, may become apparent in the older child (45). A high prevalence (20% to 30%) of chronic otitis media with middle ear effusion and fluctuating, conductive hearing loss greater than 25 dB is reported in LBW, premature infants (46). Suggested mechanisms for this relationship focus on probable eustachian tube dysfunction initiated by a combination of dolichocephalic head shape, muscular hypotonia, and prolonged nasotracheal intubation.

There have been important advances in the hearing assessment of LBW infants. Two techniques in particular, electrophysiologic auditory brain stem response (ABR) audiometry and behavioral visual reinforcement audiometry, have made early, reliable detection of hearing loss in the NICU graduate clinically feasible. Centers that routinely screen high-risk, LBW infants with ABR before nursery discharge report a false-positive rate of 8% to 10% compared to follow-up testing at 4 months of age (47). Conversely, the unanticipated appearance of severe sensorineural hearing loss in high-risk survivors of neonatal intensive care after having passed an initial ABR screening test in the newborn period has been reported (48). It also must be recognized that ABR tests only the high sound frequencies (i.e., 2,000 Hz and above) and will not detect hearing losses confined to the lower frequencies. Thus, clinicians must remember that determinations of the adequacy of hearing made only with ABR test data before nursery discharge are subject to error. Visual reinforcement audiometry is an operant conditioning technique that reliably can provide auditory thresholds for infants who are functioning at a developmental age of approximately 6 months or older. It has great utility in the high-risk follow-up clinic. A third and newer audiologic procedure, evoked otoacoustic emissions, offers promise to be of use in newborn screening in conjunction with ABR.

Visual Impairment

The major cause of visual loss in LBW infants is retrolental fibroplasia, now included under the rubric of ROP. With controlled oxygen administration, ROP was relatively rare until the last 15 years or so, when significant numbers of extremely premature infants began to survive. The name ROP recognizes that immaturity at birth is the single largest risk factor for this disease. For all practical purposes, this is a disorder of the VLBW infant. Virtually no retinal detachment and little retinal scarring is described in larger premature infants. For the entire VLBW population, current prevalence estimates range from 20% to 25% with early-stage, regressed ROP; 5% to 10% with more advanced-stage, scarred ROP; and 2% to 4% with major visual impairments, including legal blindness, requiring special educational assistance. The distribution of visually impaired infants, however, is skewed heavily toward those weighing 1,000 g or less at birth. In these ELBW infants, regressed ROP occurs in 40% to 50% of survivors, scarred ROP in 10% to 25%, and major visual impairments in 5% to 10%. Figure 59–3 shows the overall prevalence of ROP by birth weight.

Alteration of normal retinal vascular development is the hallmark of ROP. Although a great deal of effort has been invested in clinical and animal studies of ROP, there remains an etiologic maze in which no single factor stands alone (49). It appears that the embryonic retina of the small premature, developing outside the uterus, is vulnerable to many sources of disturbance that can disrupt orderly differentiation and vascularization. In addition to the well-known impact of hyperoxia, it seems that hypoxia, variations in $PaCO_2$, pH, retinal oxygen consumption, light exposure, and other factors that affect retinal perfusion all may play a role. A formula for ROP could be: immaturity (always) + oxygen (often) + other factors (variably) = ROP (50). Simply stated, the smallest

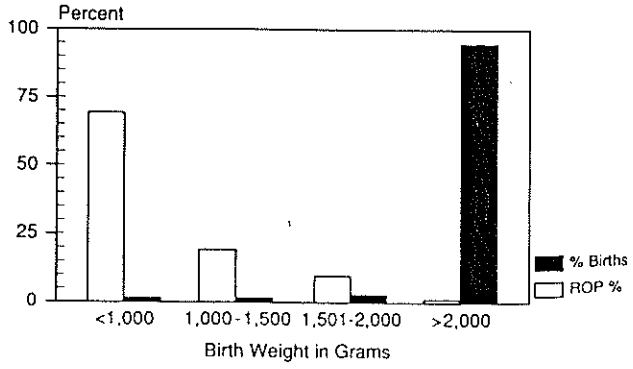

FIG. 59–3. Percentage of retinopathy of prematurity (ROP) by birth weight versus proportion of births by birth weight. (From Glass P, Avery GB, Subramanian KNS, et al. Effect of bright light in the hospital nursery on the incidence of retinopathy of prematurity. *N Engl J Med* 1985;313:401, with permission.)

and sickest newborns have the most complications that potentially can impede retinal function, and they also have the most ROP.

Even regressed ROP is associated with an increased risk for refractive errors, amblyopia, and strabismus. "Myopia of prematurity," even without ROP, has been described to occur in approximately one-third of surviving ELBW infants (51). It is considered to be mostly lenticular in origin and to improve slowly, but not completely, throughout childhood, with slight visual acuity differences still apparent in early adulthood. Strabismus may represent an isolated problem or, in some cases, may be an initial indication of a generalized neuromotor problem such as cerebral palsy. Visual and hearing impairments may coexist, and prematurity is the leading cause of children with both deficits. Monitoring of eye muscle balance and alignment and visual acuity should be part of routine follow-up of the premature infant, particularly during the preschool years. Required interventions may include eye muscle surgery, antisuppression patching, or corrective lenses.

Progressive Hydrocephalus

Depending on the reporting center, between 20% and 40% of VLBW infants have neonatal ultrasonographic evidence of intracranial hemorrhage, frequently including intraventricular hemorrhage with ventriculomegaly (10). Whereas older reports indicated discouragingly high rates of posthemorrhagic hydrocephalus, recent reports are much more hopeful in describing a very low prevalence (2% to 4%) of progressive hydrocephalus requiring ventriculoperitoneal shunting in VLBW infants (52,53). Serial scanning with cranial ultrasonography has revealed that most cases of early ventriculomegaly either spontaneously resolve or arrest. The necessity of medical intervention (e.g., repeated lumbar puncture, diuresis) to prevent the transition from relatively asymptomatic ventriculomegaly to progressive hydrocephalus remains unclear. Surgical ventriculostomy drainage is frequently employed as a temporizing procedure in more advanced cases.

For the infant in whom posthemorrhagic progressive hydrocephalus does develop, it generally becomes clinically evident between 2 and 8 weeks of age; however, appearance during late infancy occasionally has been reported. Vigilance in measurement of the head circumference at each follow-up examination of the infant is important, and obtaining a cranial ultrasound if head growth becomes substantially out of proportion to the other growth parameters may be indicated. Although the initial months of life are the time when progressive hydrocephalus is most likely to develop in premature infants, it also is the period of time when the normal phenomenon of catch-up head growth in these recovering infants becomes most apparent. Thus, increase in head circumference relative to weight and length usually is an anticipated sign rather than a pathologic one, and such awareness should guide clinical investigative decisions. When progressive hydrocephalus does occur, neurodevelopmental outcome is frequently, although not invariably, abnormal, complicated by one or more of the major disabilities (e.g., cerebral palsy, mental retardation, sensory impairments) (54).

Minor Impairments

Although major disabling sequelae are by far the easiest to quantify and report, a large and persuasive body of long-term follow-up studies clearly indicates that a broad spectrum of cognitive, behavioral, and other minor neurodevelopmental and neurobehavioral sequelae are substantially more prevalent in surviving LBW, premature infants. These morbidities become increasingly apparent in a variety of clinical manifestations with increasing age, particularly during the first 6 years of life. These early, often subtle, developmental and behavioral delays and differences are not necessarily outgrown but frequently portend future school dysfunction and may therefore become major impediments to normal academic and social progress. Collectively, these problems often are referred to as the "new morbidity" of prematurity, reflecting their more insidious nature and more intense scrutiny in recent years (23).

Specific types of developmental morbidities described in LBW cohorts include cognitive delays (i.e., lower IQ), speech and language disorders, persistent neuromotor abnormalities, including difficulties with balance and coordination, and perceptual problems. Specific areas of suboptimal behavioral style and performance include neonatal behavior, infant and toddler temperament, emotional maturity, social competence, and selective attention. As with major impairments, the overall prevalence of these minor sequelae increases with decreasing birth weight and gestational age and also is greater in male survivors. Prevalence estimates in VLBW infants vary between 15% and 25%. Accordingly, when the 15% to 20% major disability rate is combined, between 35% and 45% of VLBW survivors demonstrate a residual developmental or behavioral problem that compromises their anticipated function (55). Recent estimates for ELBW infants are in excess of 50% (56). As with major impairments, most of the minor developmental morbidities associated with LBW and prematurity also are related to the severity of perinatal–neonatal illness. That is, LBW infants who experience a prolonged hospital course with many medical complications have an increased likelihood of development of some type of developmental dysfunction. Thus, the smallest and sickest infants, particularly those ELBW new survivors of the 1990s, are the most vulnerable to experience these problems.

In the hundreds of outcome studies across multiple developmental and behavioral domains, a consistent find-

ing is that, regardless of the measures used, groups of premature children are less competent and score less well than groups of full-term children (25). However, this does not mean that individual premature children will invariably be less capable than individual full-term children. Despite the large number of significant group associations in follow-up studies, individual developmental outcome remains very difficult to predict prospectively with accuracy in the NICU, and infants with apparently similar neonatal courses may develop entirely differently.

Cognitive and Perceptual Development

Consistent deficits in performance on intelligence measures repeatedly have been observed and reported in LBW, premature children compared to FBW, full-term children (57,58). Furthermore, these differences in cognitive development become apparent in the first years of life and then persist and increase during the preschool and early school years even when the single most powerful predictor of IQ—socioeconomic status—is adequately controlled. In other words, significant deficits in cognitive and perceptual function occur frequently even in middle to upper-middle social class children born prematurely, particularly compared to their full-term peers. This important and academically relevant group difference exists despite the fact that most LBW children will have measured IQs within the average range (22).

Cognitive developmental differences between premature and full-term infants have been reported in early infancy. Rose investigated the effect of increasing familiarization time on the visual recognition memory of 6- and 12-month-old premature and full-term infants (59). Whereas the older infants showed evidence of recognition memory after less familiarization time than the younger ones, at both ages premature infants required considerably longer familiarization times (i.e., more practice) than did full-term infants. These results suggest that there are persistent differences between premature and full-term infants throughout at least the first year of life in a very fundamental aspect of cognition, namely, visual information processing.

Because manipulative exploration of objects may be important to the infant's perception and conceptualization of objects, Ruff and colleagues studied this developmental function in both premature and full-term 9-month-old infants by means of coded and scored videotapes (60). The videotapes were scored for behaviors such as looking, handling, mouthing, turning the object around, transferring the object from hand to hand, and banging. A high-risk subgroup of premature infants based on neonatal complications manipulated the objects significantly less than either the low-risk prematures or the full-term infants. There was a relationship between manipulative exploration at 9 months and later cognitive functioning at 24 months.

Low-birth-weight cognitive deficits have been described from the earliest days of neonatal intensive care and even before. Using a sample of approximately 600 children born in two Edinburgh, Scotland, hospitals in 1953 to 1955, Drillien demonstrated that IQ scores decline with decreasing birth weight in the first 4 years of life (61). The percentage of children with IQ scores below 80 at 4 years was 29% for those under 4 lb 8 oz, 13% for those between 4 lb 8 oz and 5 lb 8 oz, and 4% for those above 5 lb 8 oz. Wiener and colleagues, reporting on a sample of 417 8- to 10-year-old LBW children who had been tested with the Wechsler Intelligence Scale for Children, found that the verbal IQ, which consists of predominantly cognitive and language items, performance IQ, which consists of predominantly motor–perceptual items, and full-scale IQ, which consists of a combination of the verbal and performance scales, all showed increasing impairment with decreasing birth weight even though all subtest means remained within the average range of intelligence (62). Moreover, approximately twice as large a proportion of LBW children as FBW control children fell into the borderline IQ category (70 to 84), which usually is associated with special educational needs. Visual–motor–perceptual skills, as measured independently by the Bender Gestalt Test, also varied directly with birth weight. Hunt and colleagues reported the following cognitive outcome proportions in a cohort of 108 VLBW children at 8 years of age: 4.6% had a very low IQ (<70), 13.9% had a low IQ (70 to 84), and, for those with an IQ greater than 84, 12.0% had language disability, 12.0% had performance disability, 21.4% had visual–motor disability, and 36.1% were apparently normal (63).

In a Vancouver, British Columbia, study of 501 LBW and 203 FBW children born between 1958 and 1965, the IQ difference between LBW and FBW groups on the Stanford–Binet Intelligence Scale was 9 points at 30 months of age and 15 points at 48 months, even after exclusion of children with major cerebral deficit or IQ scores under 50 or significant visual problems (57). In both the Edinburgh and Vancouver studies, the poor functioning of LBW children is convincingly exacerbated in socioeconomically disadvantaged subgroups. Table 59–5 illustrates this interaction of both biological and environmental risk factors in the determination of measured IQ of the Vancouver study children. At both 2.5 and 4 years of age, FBW, highest-social-class children earned the highest subgroup mean IQ score, whereas LBW, lowest-social-class children earned the lowest. Both FBW and LBW groups demonstrated an IQ score continuum from the highest social class, which had the highest mean IQ, to the lowest social class, which had the lowest mean IQ, with the FBW subgroup always higher than the LBW regardless of social class; at 4 years of age, even FBW, lowest-social-class children scored higher than their LBW, highest-social-class peers.

TABLE 59–5. *Comparison of intelligence quotient means for low-birth-weight children versus normal-birth-weight controls within social class groups*

Hollingshead social class	Statistic	30 Months of age		48 Months of age	
		IQ	Number	IQ	Number
I, II, III	LBW[a] mean±SD	97.0±15.1	48	99.5±13.7	67
	Control mean±SD	108.8±8.2	19	118.3±11.4	26
	Difference±SE	11.8±2.9		18.8±2.8	
	p	<0.001		<0.001	
IV	LBW mean±SD	91.7±10.7	59	94.3±11.3	100
	Control mean±SD	102.9±12.6	43	110.0±16.8	58
	Difference±SE	11.2±2.4		15.7±2.5	
	p	<0.001		<0.001	
V	LBW mean±SD	89.5±13.9	52	90.6±15.8	79
	Control mean±SD	96.0±9.7	32	102.3±12.9	42
	Difference±SE	6.5±2.6		11.7±2.7	
	p	<0.01		<0.001	

[a]LBW, low birth weight; FBW, full birth weight; IQ determined from Stanford–Binet tests.
Adapted from McBurney AK, Eaves LC. Evolution of developmental and psychological test scores. In: Dunn HG, ed. *Sequelae of low birthweight: the Vancouver Study.* Philadelphia: JB Lippincott, 1986:61.

The cognitive performance of ELBW preschool children has been the subject of more recent attention. Halsey and colleagues compared predominantly white, middle-class ELBW 4-year olds to matched full-term children and also to matched LBW children (1,500 to 2,500 g birth weight) and found both comparison groups to be two-and-a-half times more likely to have optimal development (64). Comparison children had mean cognitive scores 15 to 18 points higher than ELBW children. The investigators concluded that weaker performance on all study measures (i.e., language, motor, memory, visual–motor, perceptual) exists before school entry among nondisabled ELBW children compared with their peers. Breslau and colleagues confirmed these cognitive concerns for ELBW survivors in describing a gradient relationship between LBW and IQ at age 6 years (65). They found the largest deficit in full-scale IQ in those children born weighing 1,500 g or less, an intermediate deficit in those born weighing 1,501 through 2,000 g, and the least pronounced deficit in those born weighing 2,001 through 2,500 g.

Language Development

Communication skills involving auditory and visual perception, the learning and conceptualizing of a verbal symbol system (i.e., language), and the actual production of speech are critical to academic learning and social adjustment. Several investigations have focused exclusively on this important area of development in premature infants. Zarin-Ackerman and colleagues noted both receptive and expressive language deficiencies at 2 years of age in a group of children born as at-risk (i.e., predominantly premature) infants compared to others born as healthy, full-term infants (66). They emphasized that these deficits could not be a function of social class, which is a major factor influencing language development, because this variable was controlled. In Switzerland, Largo and associates compared 114 premature children to 97 healthy, full-term children throughout the first 5 years of life (67). Most stages of language development occurred at slightly later ages among the premature children than among those born at term. Birth weight and gestational age were negatively correlated with language development at all ages. Perinatal–neonatal complications also were significantly negatively correlated with the ages at which the stages of language development were reached, and also with final language performance at 5 years of age. There were no significant differences in socioeconomic status between the premature and full-term groups. The particular demographics of this unique study allowed the authors to conclude that biomedical factors exert a considerable effect on the early language development of premature children and that this effect is greater than previously had been recognized (67).

Several smaller studies have confirmed the existence of linguistic dysfunctions among premature children, particularly those with complicated neonatal courses (68,69). On the basis of a wide variety of measures, inferior performance has been reported consistently in receptive language or comprehension, expressive language parameters such as vocabulary and word finding, and speech qualities such as articulation and fluency.

Motor Development

Numerous studies from several continents repeatedly have documented that the neuromotor development of LBW, premature infants during the first 2 years of life is different, more delayed, and generally more worrisome

than that of healthy, full-term infants. Not only are premature developmental scores, using such measures as the Bayley Scales of Infant Development, consistently and significantly below those of full-term infants at 12 months of corrected age but premature motor scores also usually are 10 to 15 points (i.e., practically one standard deviation) below premature mental scores at this age (70).

This phenomenon of transiently abnormal neuromotor signs in the first years of life was described initially by Drillien, in a 1972 report from Scotland, as "transient dystonia of low birth weight infants" (71). Drillien reported that its prevalence during the first one-half of infancy varied inversely with birth weight, involving approximately 35% of infants weighing 1,501 to 2,000 g at birth and 60% to 70% of infants weighing 1,500 g or less at birth, and that its prevalence also varied directly with perinatal–neonatal complications (i.e., more frequent among sick premature infants). Transient dystonia includes such neurologic findings as increased or decreased muscle tone, diminished volitional movement, retention and accentuation of primitive reflex patterns, delayed appearance of normal infantile automatic reactions, and asymmetric neuromotor development. Because these neuromotor signs also are the very signs seen in infants in whom cerebral palsy is developing, it is not surprising that a reliable diagnosis of cerebral palsy is quite difficult in most premature infants throughout early infancy. As described by Amiel-Tison, however, by 8 to 10 months of corrected age, most LBW infants with transient dystonia are gradually and spontaneously normalizing on examination, whereas those relatively few infants in whom permanent cerebral palsy is developing appear increasingly abnormal (72). With the knowledge of this common evolution of neuromotor signs, every VLBW infant can be assigned to one of three diagnostic and prognostic groups at 12 months of age: those who were always neurologically normal throughout infancy (25% to 30%); those who showed transient dystonia with subsequent normalization (65% to 70%); and those with cerebral palsy (5% to 10%).

Coolman and colleagues and others have extended these observations to 24 months of age, albeit most neuromotor changes occur in the first year of life (73). They found that some infants with transient dystonia retained subtle, persistent neuromotor differences that would not be labeled as cerebral palsy but that represented qualitative deviations from the norm. Longitudinal studies indicate that infants who have experienced transient dystonia are far more likely to have language, learning, and behavioral problems (i.e., minimal brain dysfunction) in later childhood than are infants who never demonstrated these abnormalities (74,75). This would indicate that although transient dystonia largely resolves, these neuromotor signs in early infancy may be predictive markers for later manifestations of central nervous system disorganization.

Differences in the motor development of premature infants throughout the preschool years have been reported. Burns and Bullock found premature children at 5 years of age to be significantly different from their full-term peers in terms of tremulous involuntary hand movements, less competent gross motor ability, and difficulties in postural control and balance (76). Crowe and associates described ELBW infants as a group to have significantly inferior skills in all motor functions at 4 years of age (77). Symptomatic intracranial hemorrhage was associated with poorer motor performance.

Neurobehavioral Development

As LBW, premature survivors are assessed more critically and at older ages, a variety of potential behavioral dysfunctions throughout infancy and childhood become evident. Numerous studies have compared the neonatal neurobehavioral performance of LBW infants to that of FBW infants. These studies typically compare premature infants at their corrected age and also tend to use premature infants with relatively uncomplicated neonatal courses. Nevertheless, despite these sampling features that might obscure group differences, premature infants consistently perform less optimally than healthy, full-term infants on these early measures.

Ferrari and colleagues compared low-risk premature infants to healthy, full-term infants using the Brazelton Neonatal Behavioral Assessment Scale (78). They found the premature infants to be significantly inferior in sensory orientation, regulation of behavioral state (i.e., quiet–active status), and autonomic regulation. Additionally, the clustering of neurobehavioral items was more heterogeneous among premature infants. The authors concluded that prematurity itself is associated with a behavioral repertoire that is different, more variable, and on the average less competent than that of full-term infants (78). Friedman and colleagues, also comparing low-risk premature infants and healthy, full-term infants, found that the premature infants fussed and cried more, were less soothable, and tended to change behavioral state more frequently (79). They suggested that these neonatal neurobehavioral differences are potential contributors to suboptimal interaction between premature infants and their caregivers. Aylward and colleagues, in a report from the National Institutes of Health (NIH) Collaborative Study on Antenatal Steroid Therapy, reported significant effects of both gestational age and severity of perinatal–neonatal illness on the neurobehavioral responses of premature infants (80). Specifically, at 40 weeks of corrected age, premature infants born at younger gestational ages and with greater medical complications demonstrated altered behavior in terms of diminished spontaneous activity and vigor, inability to maintain and modulate responses, and poorer visual orientation capabilities.

A number of studies using a wide variety of electrophysiologic techniques have supported the results of these clinical behavioral investigations. Compared to full-term infants, premature infants have been shown to

have delayed maturation of both cortical and brainstem auditory evoked potentials, more variable and labile behavioral state organization as measured by time-lapse videosomnography, and decreased resting heart rate variability and vagal tone (i.e., an indirect measure of overall autonomic nervous system activity) (81–84). Several of these functions, particularly state organization and autonomic regulation, have been related positively to longer-term developmental outcome (85,86).

Several studies have explored the related behavioral areas of temperament, social interaction and competence, and emotional expression and affect. Most of these studies have examined mother–infant interactions, and there is an overall consensus of findings that indicates an imbalance in LBW, premature dyads compared to FBW, full-term dyads, with LBW infants typically less responsive and low in communicative signaling behavior, and their mothers compensating for this relative inactivity by displaying high levels of stimulating and engaging activity. Investigations of LBW infants with complicated perinatal–neonatal courses have indicated that these infants exhibit high levels of gaze aversion, avoidance of interaction, and low levels of vocalizing and playing (87–89). Field has reported these interactional differences in depth and succinctly summarizes the problem: "High risk infants and their parents have less fun' than normal infants and their parents during their early interactions together" (90). In a study comparing premature–mother dyads with full-term–mother dyads at approximately 4 months of corrected age, Field found the premature infants to be less alert and attentive, less responsive, less interested in game playing, less contingent, less smiling and content, and more affectively negative and irritable than the matched full-term infants. Correspondingly, the mothers of prematures exhibited fewer happy expressions than the mothers of full-terms but were more vocal as they attempted to elicit social and communicative responses from their infants.

Crnic and associates (91) and Malatesta and colleagues (92) have replicated and extended these observations throughout the entire first year of life; LBWFBW differences in expressive behavior and affect were persistent and continued to affect maternal behavior. Malatesta and colleagues emphasized that in their primarily middle to upper-middle social class sample, these differences were seen even in the absence of confounding neonatal medical complications. They speculate that the observed LBWFBW differences probably are even more pronounced with less advantaged, more stressed, or sicker premature infants. Of long-term importance and concern is the increasing evidence of continuity between early interactional disturbances and later behavioral dysfunctions.

School Function

Finally, as increasing numbers of studies have followed LBW, premature infants into the school years, the full spectrum of these children's learning and behavioral performance is emerging and becoming clearer. Although prevalence estimates of school problems vary between reports, almost all investigators agree that LBW survivors have a distinctly increased risk for school dysfunction in some form (23). The most recent reports have focused on school-age ELBW children and consistently describe the most problematic school function of all. Again, these new survivors, although relatively small in overall number, are disproportionately represented in regard to academic and social failure. There also is general agreement that although this substantial risk exists independently of socioeconomic status, the combination and interaction of biologic and environmental risks produces an especially worrisome doubly vulnerable milieu and a highly appropriate target population for early developmental intervention efforts because of the documented importance of psychosocial variables in the ultimate prognosis for LBW, premature infants (93).

Dunn and colleagues, in one of the most extensive longitudinal follow-up studies published, reported minimal cerebral dysfunction (i.e., minor developmental and behavioral abnormalities) to be the single most prevalent (20%) disabling syndrome at school age in a population of over 300 LBW, premature children (94). Furthermore, the authors stress the difficulty in adequately predicting or identifying such dysfunctions before school entry at the age of 5 years (94). This important group of sequelae consequently is liable to be missed when the outcome of NICU graduates is assessed before that age. Figure 59–4 illustrates this diagnostic evolution and increase in developmental–behavioral problems over time. As in other studies, this study found a disproportionate number of boys compared to girls who experienced school dysfunction and required remedial assistance. This investigation was continued into adolescence (95). Although several of the LBW children with earlier problems no longer were demonstrating all of them, an almost equal number of previously unrecognized children had manifested academic and social problems, thus resulting in a relatively stable number of such problems over time. Additionally, whereas behaviors such as overactivity, temper tantrums, and perseveration had greatly subsided, symptoms of neuropsychiatric disturbance, including distractibility, irritability, unhappiness, low frustration tolerance, fears, disobedience, poor motivation, and sleep difficulties, persisted or increased.

Other studies have confirmed these observations in VLBW children at 8 to 15 years of age and have documented, in such areas as verbal expression, academic achievement, social competence, and emotional maturity, continued problems that cannot be attributed primarily to social class or differences in the quality of parenting (96,97). Nickel and colleagues evaluated the school performance at a mean age of 10 years of 25 ELBW children who were cared for at a time (1960–1972) when only very

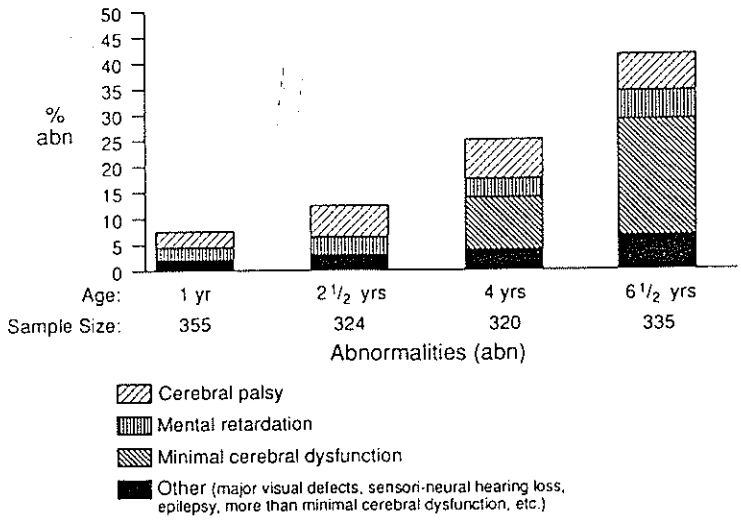

FIG. 59–4. Evolution of developmental dysfunction in low-birth-weight, premature children. (Adapted from ref. 94, with permission.)

premature infants who had little or no neonatal illness survived (98). Despite an overall mean IQ of 90 (range 50 to 141), 16 (64%) of these children had been or currently were in special educational programs. Only seven (28%) were rated by their teachers to be achieving at or above grade level. Arithmetic reasoning, mathematics achievement, reading comprehension, balance, fine motor coordination, and perceptual function were specific and common weaknesses for these children.

Klein and associates compared 65 9-year-old children born in Cleveland, Ohio, in 1976, who were VLBW and who were free of neurologic impairment, to 65 FBW children who had been matched for age, gender, race, and social class on measures of IQ, visual–motor and fine motor abilities, and academic achievement (99). The following were the major findings:

- The VLBW children scored significantly lower than the FBW children on tests that measure general intelligence, even though both group means were within the average range.
- The VLBW children scored significantly lower than the FBW children on tests that measure academic achievement.
- The VLBW children had particular deficits in mathematics achievement.
- The VLBW children had particular deficits on tests that involve visual or spatial skills.
- These results were independent of social class.

In a similarly controlled and longitudinal New York City study, Ross and colleagues showed that a much higher proportion of 8-year-old VLBW children required special educational interventions (48%) than either FBW children (15%) or the New York State public elementary school population (10%) (100). Very-low-birth-weight children scored significantly lower than FBW children on tests of IQ, verbal ability, academic achievement, and auditory memory. There was an interaction of prematurity and social class on IQ, verbal tests, academic achievement, and attention, with premature children of lower socioeconomic status scoring lowest on these measures.

A number of more recent reports emphasize the school problems of ELBW children. From an analysis by birth weight subgroups, Klebanov and colleagues indicated that as birth weight decreases, the prevalence of grade failure, placement in special classes, and classification as impaired increases, even when maternal education and neonatal length of stay are controlled for (101). The ELBW children scored lower than all other birth-weight groups on math and reading achievement tests. Even among children with IQ scores above 85, ELBW children still obtained lower math scores than the other children. Even with optimal socioeconomic environments, approximately one of every two ELBW children requires special educational services (102). In a Scottish population-based sample of 8-year-old children, ELBW children placed heavy demands on regular schools, with 52% requiring learning support compared with 16% of FBW comparison children (103). Hack and colleagues have delineated school-age outcomes in ELBW children with birth weights under 750 g (Fig. 59–5) (56). Compared with VLBW children weighing 750 to 1,499 g at birth and also to FBW children, these markedly ELBW children were inferior in cognitive ability, psychomotor skills, and academic achievement. They had poorer social skills and adaptive behavior and more behavioral and attention problems. In all assessed areas, the functioning of VLBW children was intermediate between that of ELBW and FBW children.

Although data on the prevalence of behavior problems in older LBW children are somewhat sparse, it is likely that the prevalence is substantially higher than in FBW children. For example, Escalona found that 30% of a primarily disadvantaged premature sample exhibited major

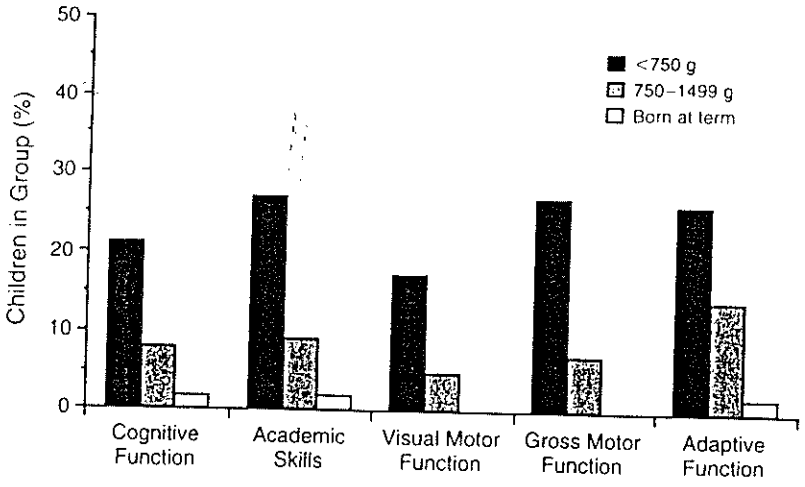

FIG. 59–5. Percentage of children in each study group with subnormal functioning. (From ref. 56, with permission.)

behavior problems before the age of 4 years (104). The most comprehensive investigation of long-term behavioral function in this population comes from the same Cleveland, Ohio cohort described in terms of academic achievement (99). Breslau and colleagues compared 65 9-year-old VLBW children to 65 FBW children, matched for age, gender, race, social class, and school, on parents' ratings on the Child Behavior Checklist and teachers' ratings on the Teacher's Report Form (105). Results from parents and teachers converged on key findings. The major findings were the following:

The VLBW boys manifested significantly more behavioral disturbance and poorer social competence than FBW boys.

The excess in behavior problems in VLBW boys spanned over a wide range of behavioral domains, including both internalizing (e.g., depressive–anxious) and externalizing (e.g., hyperactive, aggressive, conduct problems) syndromes.

The effect of VLBW on behavior problems and social adjustment in boys was not a function of IQ.

These results were independent of social class.

Although VLBW girls did not differ significantly from FBW girls, suggestive trends in the same direction as the boys may indicate that there is an increased risk for behavior problems in both genders but that these sequelae become evident at an earlier age in boys than in girls.

As in other neurodevelopmental and neurobehavioral domains, Klebanov and colleagues found that ELBW children had lower attention, language skills, overall social competence, scholastic competence, and athletic ability than all other birth-weight groups (very low, low, and normal) as measured by classroom teachers, even when neonatal length of stay, child's gender and ethnicity, and maternal education were controlled for (106). The classroom behavior of ELBW children was rated by teachers as poor, even for children who had not failed a grade.

SPECIFIC PERINATAL–NEONATAL COMPLICATIONS IN HIGH-RISK INFANTS

Intrauterine Growth Retardation

The SGA infant has a higher mortality rate, a higher incidence of perinatal–neonatal complications, and a higher prevalence of chronic neurologic impairments than the appropriate-for-gestational-age (AGA) infant of similar gestational age (107). The diagnosis of SGA is useful in identifying a high-risk population needing careful follow-up; however, the population of SGA infants is a heterogeneous one with multiple etiologies. Intrauterine growth pattern, associated congenital anomalies, mortality rate, risk of perinatal–neonatal complications, and long-term outcome reflect not only the nature of the insult but the timing as well. Drillien and colleagues have stressed the need to differentiate early-pregnancy-onset SGA infants, many of whom demonstrate intrinsic defects such as congenital anomalies, from late-pregnancy-onset SGA infants, who may have antenatal histories of placental insufficiency or maternal chronic illness (74). Long-term developmental prognosis, in terms of major and minor impairments and school function, is significantly worse for early-pregnancy-onset SGA infants.

Most SGA outcome studies also distinguish between full-term and premature SGA infants because of marked differences in mortality and morbidity rates, both of which are significantly higher for premature SGA infants. For both groups of SGA infants, great variability among outcome studies is the norm, again reflecting the inevitable heterogeneity of the SGA diagnosis. Many studies report few major neurologic disabilities in full-term SGA infants followed from birth. In 96 full-term SGA infants followed to the age of 5 years, Fitzhardinge and Stevens reported only a 1% prevalence of cerebral palsy and a 6% prevalence of seizures (108). In a cerebral-palsied population in Sweden, full-term SGA infants had a somewhat higher risk for cerebral palsy than full-term AGA infants but a

much lower risk than premature AGA and premature SGA infants (37). Most full-term SGA infants are of average intelligence, whether tested during the preschool or school years, even though the mean IQ of the SGA population usually has been somewhat lower than that of control groups (109). Fitzhardinge and Stevens, however, found that, despite average intelligence, 50% of the SGA boys and 36% of the SGA girls were doing poorly in school. One-third of the SGA children with IQs above 100 were failing consistently at school. A history of perinatal asphyxia was an important contributing risk factor. Other studies provide good evidence of an increased prevalence of speech and language problems, minor neurologic findings, and attention deficits in this subgroup (110).

Relatively few studies evaluate the outcome of premature SGA infants, and the results are contradictory. The prevalence of reported impairments varies from nearly 50% to as low as 10%. Commey and Fitzhardinge found that 15% of premature SGA infants had cerebral palsy at the age of 2 years, twice the prevalence encountered in premature AGA infants (111). In the Swedish cerebral palsy study, premature SGA infants had the highest risk for cerebral palsy, 15 times greater than full-term AGA infants and significantly more than full-term SGA and premature AGA infants (37). Commey and Fitzhardinge found a high prevalence of subnormal intelligence in premature SGA infants tested at the age of 2 years. Drillien reported that, in all birth-weight subgroups, fewer premature SGA infants were average cognitively, and more had borderline intelligence or mental retardation, especially those born to parents of low socioeconomic status (112).

There is little specific information about school function in this subgroup, but premature SGA infants certainly must be presumed to be at substantial risk in this area as well. A recent report compared the cognitive and neurologic outcomes of 129 premature SGA infants with 300 premature AGA infants through 6 years of age (113). The SGA infants had significantly poorer cognitive scores at each assessment age than AGA infants of similar gestational ages. Normal neurologic status was more likely at all assessments for the AGA than for SGA infants of comparable gestational age. Nevertheless, there was a significant effect of SGA on cognitive outcome at school age independent of neurologic status.

Asphyxia

Hypoxic–ischemic brain injury is the single most important neurologic problem occurring in the perinatal period (114). This variety of brain injury accounts for many, although not the majority, of the severe, nonprogressive neurologic deficits seen in children. This is particularly the case for full-term infants but also is of etiologic significance for premature infants. The neurodevelopmental deficits of concern are principally the triad of cerebral palsy, mental retardation, and epilepsy, often occurring together in varying degrees. In addition, more subtle developmental and behavioral dysfunctions in the areas of language, fine motor coordination, socioemotional competence, attention, and school learning are increasingly recognized in the relatively few studies designed to investigate these long-term sequelae. The common denominator of this form of brain injury is deprivation of the supply of oxygen to the central nervous system. The developing brain can be deprived of oxygen by two major pathogenetic mechanisms—hypoxemia (i.e., diminished amount of oxygen in the blood supply) or ischemia (i.e., diminished amount of blood perfusing the tissue). These two overlapping mechanisms typically coexist clinically, are virtually impossible to isolate and delineate precisely in the individual infant, and together constitute the basis of the syndrome of asphyxia (115).

As noted by Paneth and Stark, the fundamental problem in assessing the exact relationship between asphyxia and subsequent neurodevelopmental outcome has been the difficulty in assessing the degree of asphyxia (116). Various techniques have been used to identify the asphyxiated infant, including the time to initiate spontaneous respiration (<1 minute), the time that positive-pressure ventilation was required to sustain the infant (<1 minute), and the use of the neonatal scoring system developed by Virginia Apgar (117). This scoring system originally was created to identify infants who were physiologically depressed at birth and who required resuscitative efforts. It has been shown to have limited utility in premature infants (118). Although Apgar did not design the scoring system to be used as a tool to predict long-term neurologic status, it has been used by many for correlation with ultimate outcome because of the paucity of alternative asphyxial markers. Fetal scalp blood and umbilical cord blood sampling for pH and other acid–base parameters have been recommended as potentially providing more objective perinatal data.

Although the Apgar scoring system is not perfect, it continues to be the standard by which almost all neonates are evaluated immediately after birth, and, as such, was the perinatal measure used in the NIH National Collaborative Perinatal Project between 1959 and 1966. This multisite prospective study of more than 50,000 pregnant woman and their children remains the largest single resource for investigating the associations between perinatal asphyxia and neurodevelopmental outcome, particularly cerebral palsy. Several main conclusions emerge (119):

Cerebral palsy does not develop in most (95%) asphyxiated full-term infants with an Apgar score ≤3 at 5 minutes.

As the duration of severe asphyxia increases from 5 to 20 minutes, the likelihood of neonatal death or permanent cerebral palsy also increases in parallel fashion; approximately 60% cerebral palsy prevalence exists in full-term survivors with Apgar scores of ≤3 at 20 minutes.

: more premature the infant, the greater the incidence
.e., approximately 30% at 28 weeks of gestational
ge), severity, and mortality associated with perinatal
sphyxia.
st infants in whom cerebral palsy develops were not
sphyxiated at birth.

Although perinatal asphyxia certainly is an important
se of severe psychomotor retardation, especially dur-
the intrapartum period, its relative contribution to
se adverse outcomes has, in the past, frequently been
rstated. It is estimated that between 10% and 20% of
cases of cerebral palsy are attributable to intrapartum
hyxia. Many of these cases are complicated by mental
rdation of variable severity. Freeman and Nelson cor-
ly emphasize the four necessary criteria to link
sally intrapartum asphyxia and neurodevelopmental
bility in full-term infants (120):

Intrapartum abnormalities (e.g., nonreassuring fetal heart rate patterns, passage of meconium, hemorrhage)
Depression at birth (e.g., low Apgar scores, need for resuscitation)
Neonatal hypoxicischemic encephalopathy (e.g., seizures in the first 48 hours, hypotonia and lethargy, metabolic acidosis, apnea)
Anticipated outcomes (e.g., cerebral palsy with associated deficits, not severe mental retardation or epilepsy by themselves).

Outcome studies in full-term infants have identified
neonatal factors most predictive of neurodevelopmen-
disability after an episode of intrapartum asphyxia.
e key predictors include failure to establish sponta-
ous respiration by 5 minutes, onset of seizures within
first 12 hours and refractory to treatment, prolonged
p encephalopathy (i.e., Sarnat stage 3) (121), failure
the electroencephalogram to normalize by 5 to 7 days,
d inability to establish adequate oral feedings by 1
ek of age (122). Fitzhardinge and colleagues described
predictive utility of the computed tomography scan
tween 1 and 2 weeks after birth (123). The most omi-
us findings were diffuse hypodensities throughout both
white and gray matter and extensive intraparenchymal
intraventricular hemorrhage. Byrne and associates
ported that 8 months of age appears to be the earliest
ne at which magnetic resonance imaging findings (e.g.,
layed myelination, acquired structural abnormalities)
rrelate well with later adverse neurodevelopmental out-
me in this populatio (124). Finally, Robertson and col-
gues compared 145 asphyxiated full-term children
o had experienced neonatal encephalopathy with a
ilar number of nonasphyxiated peer children at 8
rs of age (125). The prevalence of major impairment,
ich included cerebral palsy, mental retardation,
lepsy, cortical blindness, and severe hearing loss, was
16%. Intellectual, visualmotor integration, and receptive vocabulary scores, as well as reading, spelling, and arithmetic grade levels for those children with moderate or severe encephalopathy were significantly below those in the mild encephalopathy or peer comparison groups. Thus, children who survive moderate or severe neonatal asphyxial encephalopathy are at increased risk for both major neurosensory impairment and reduced school performance.

REFERENCES

1. McCormick MC. The contribution of low birthweight to infant mortality and childhood morbidity. *N Engl J Med* 1985;312:82.
2. Philip AGS, Little GA, Polivy DR, et al. Neonatal mortality risk for the 80s: the importance of birthweight/gestational age groups. *Pediatrics* 1981;68:122.
3. Paneth N, Kiely JL, Wallenstein S, et al. Newborn intensive care and neonatal mortality in low birthweight infants: a population study. *N Engl J Med* 1982;307:149.
4. Buehler JW, Kleinman JC, Hogue CJR. Birthweight-specific infant mortality, United States, 1960 and 1980. *Public Health Rep* 1987; 102:151.
5. Herdman RC, Behney CJ, Wagner JL, et al. *Neonatal intensive care for low birthweight infants: costs and effectiveness. Health Technology Case Study 38, Publication OTA-HCS-38.* Washington, DC: Office of Technology Assessment, 1987.
6. Hack M, Fanaroff AA. Outcomes of extremely low birthweight infants between 1982 and 1988. *N Engl J Med* 1989;321:1642.
7. Phelps DL, Brown DR, Tung B, et al. 28-day survival rates of 6,676 neonates with birthweights of 1250 grams or less. *Pediatrics* 1991; 87:7.
8. Hack M, Friedman H, Fanaroff AA. Outcomes of extremely low birth weight infants. *Pediatrics* 1996;98:931.
9. Ginsberg HG, Goldsmith JP, Stedman CM. Intact survival and 20month follow-up of a 380-gram infant. *J Perinatol* 1990;10:330.
10. Hack M, Horbar JD, Malloy MH, et al. Very low birthweight outcomes of the National Institute of Child Health and Human Development Neonatal Network. *Pediatrics* 1991;87:587.
11. Lasky RE, Tyson JE, Rosenfeld CR, et al. Disappointing follow-up findings for indigent high-risk newborns. *Am J Dis Child* 1987; 147:100.
12. Bennett FC, Robinson NM, Sells CJ. Growth and development of infants weighing less than 800 grams at birth. *Pediatrics* 1983;71:319.
13. Hoffman EL, Bennett FC. Birthweight less than 800 grams: changing outcomes and influences of gender and gestation number. *Pediatrics* 1990;86:27.
14. LaPine TR, Jackson JC, Bennett FC. Outcome of infants weighing less than 800 grams at birth: 15 years experience. *Pediatrics* 1995;96:479.
15. Shy KK, Luthy DA, Bennett FC, et al. Effects of electronic fetal heart rate monitoring, as compared with periodic auscultation, on the neurologic development of premature infants. *N Engl J Med* 1990;322:588.
16. The HIFI Study Group. High-frequency oscillatory ventilation compared with conventional intermittent mechanical ventilation in the treatment of respiratory failure in preterm infants: neurodevelopmental status at 16 to 24 months of postterm age. *J Pediatr* 1990;117:939.
17. Aylward GP, Pfeiffer SI, Wright A, et al. Outcome studies of low birthweight infants published in the last decade: a metaanalysis. *J Pediatr* 1989;115:515.
18. Blackman J. *Warning signals: basic criteria for tracking at-risk infants and toddlers.* Washington, DC: National Center for Clinical Infant Programs, 1986.
19. Blackman JA, Hein HA. Iowa's system for screening and tracking high-risk infants. *Am J Dis Child* 1985;139:826.
20. TeKolste KA, Bennett FC. The high risk infant: transitions in health, development, and family during the first years of life. *J Perinatol* 1987;7:368.
21. Barrera ME, Rosenbaum PL, Cunningham CE. Corrected and uncorrected Bayley scores: longitudinal developmental patterns in low and high birthweight infants. *Infant Behav Dev* 1987;10:337.

22. McCormick MC. long-term follow-up of infants discharged from neonatal intensive care units. *JAMA* 1989;261:1767.
23. Bennett FC. Neurodevelopmental outcome in low birthweight infants: the role of developmental intervention. *Clin Crit Care Med* 1988; 13:221.
24. Brothwood M, Wolke D, Gamsu H, et al. Prognosis of the very low birthweight baby in relation to gender. *Arch Dis Child* 1986;61:559.
25. Bennett FC, Scott DT. Long-term perspective on premature infant outcome and contemporary intervention issues. *Semin Perinatol* 1997; 21:190.
26. Paneth N, Kiely JL, Stein Z, et al. Cerebral palsy and newborn care: III. Estimated prevalence rates of cerebral palsy under differing rates of mortality and impairment of low birthweight infants. *Dev Med Child Neurol* 1981;23:801.
27. Hagberg B, Hagberg G, Olow I, et al. The changing panorama of cerebral palsy in Sweden: V. The birth year period 1979–82. *Acta Paediatr Scand* 1989;78:283.
28. Blaymore-Bier J, Pezzullo J, Kim E, et al. Outcome of extremely low-birth-weight infants: 1980–1990. *Acta Paediatr* 1994;83:1244.
29. Robertson CMT, Hrynchyshyn GJ, Etches PC, et al. Population-based study of the incidence, complexity, and severity of neurologic disability among survivors weighing 500 through 1250 grams at birth: A comparison of two birth cohorts. *Pediatrics* 1992;90:750.
30. O Shea TM, Klinepeter KL, Goldstein DJ, et al. Survival and developmental disability in infants with birth weights of 501 to 800 grams, born between 1979 and 1994. *Pediatrics* 1997;100:982.
31. Pharoah PO, Cooke T, Cooke RW, et al. Birthweight specific trends in cerebral palsy. *Arch Dis Child* 1990;65:602.
31a. Freud S. *Infantile cerebral paralysis*. Russin LA, trans. Coral Gables, FL: University of Miami Press, 1968.
32. Bennett FC, Chandler LS, Robinson NM, et al. Spastic diplegia in premature infants: etiologic and diagnostic considerations. *Am J Dis Child* 1981;135:732.
33. Volpe JJ. Cognitive deficits in premature infants. *N Engl J Med* 1991; 325:276.
34. Graziani LJ, Pasto M, Stanley C, et al. Neonatal neurosonographic correlates of cerebral palsy in preterm infants. *Pediatrics* 1986;78:88.
35. Bozynski ME, Nelson MN, Genaze D, et al. Cranial ultrasonography and the prediction of cerebral palsy in infants weighing ≤ 1200 grams at birth. *Dev Med Child Neurol* 1988;30:342.
36. Perlman JM, Risser R, Broyles RS. Bilateral cystic periventricular leukomalacia in the premature infant: Associated risk factors. *Pediatrics* 1996;97:822.
37. Hagberg B. Epidemiological and preventive aspects of cerebral palsy and severe mental retardation in Sweden. *Eur J Pediatr* 1979;130:71.
38. Gibson RL, Jackson JC, Twiggs GA, et al. Bronchopulmonary dysplasia: survival after prolonged mechanical ventilation. *Am J Dis Child* 1988;142:721.
39. Singer L, Yamashita T, Lilien L, et al. A longitudinal study of developmental outcome of infants with bronchopulmonary dysplasia and very low birth weight. *Pediatrics* 1997;100:987.
40. Bradford BC, Baudin J, Conway MJ, et al. Identification of sensory neural hearing loss in very preterm infants by brainstem auditory evoked potentials. *Arch Dis Child* 1985;60:105.
41. de Vries LS, Lary S, Dubowitz LMS. Relationship of serum bilirubin levels to ototoxicity and deafness in high-risk low birthweight infants. *Pediatrics* 1985;76:351.
42. Salamy A, Eldredge L, Tooley WH. Neonatal status and hearing loss in high-risk infants. *J Pediatr* 1989;114:847.
43. Leavitt AM, Watchko JF, Bennett FC, et al. Neurodevelopmental outcome following persistent pulmonary hypertension of the neonate. *J Perinatol* 1987;7:288.
44. Abramovich SJ, Gregory S, Slemick M, et al. Hearing loss in very low birthweight infants treated with neonatal intensive care. *Arch Dis Child* 1979;54:421.
45. Bess FH, Tharpe AM. Unilateral hearing impairment in children. *Pediatrics* 1984;74:206.
46. Thompson G, Folsom R. Hearing assessment of at-risk infants. *Clin Pediatr* 1981;20:257.
47. Marshall RE, Reichert EJ, Kerley SV, et al. Auditory function in newborn intensive care unit patients revealed by auditory brainstem potentials. *J Pediatr* 1980;96:731.
48. Nield TA, Schrier S, Ramos AD, et al. Unexpected hearing loss in high-risk infants. *Pediatrics* 1986;78:417.
49. Avery GB, Glass P. Retinopathy of prematurity: progress report. *Pediatr Ann* 1988;17:528.
50. Avery GB, Glass P. Retinopathy of prematurity: what causes it? *Clin Perinatol* 1988;15:917.
51. Scharf J, Zonis S, Zeltzer M. Refraction in premature babies: a prospective study. *J Pediatr Ophthalmol Strabismus* 1978;15:48.
52. Camfield PR, Camfield CS, Allen AC, et al. Progressive hydrocephalus in infants with birthweights less than 1500 grams. *Arch Neurol* 1981;38:653.
53. Shinnar S, Molteni RA, Gammon K, et al. Intraventricular hemorrhage in the premature infant. *N Engl J Med* 1982;306:1464.
54. Chaplin ER, Goldstein GW, Myerberg DZ, et al. Posthemorrhagic hydrocephalus in the preterm infant. *Pediatrics* 1980;65:901.
55. Saigal S, Rosenbaum P, Stoskopf B, et al. follow-up of infants 501 to 1500 gm birthweight delivered to residents of a geographically defined region with perinatal intensive care facilities. *J Pediatr* 1982;100:606.
56. Hack M, Taylor HG, Klein N, et al. School-age outcomes in children with birth weights under 750 g. *N Engl J Med* 1994;331:753.
57. McBurney AK, Eaves LC. Evolution of developmental and psychological test scores. In Dunn HG, ed. *Sequelae of low birthweight: the Vancouver study*. Philadelphia: JB Lippincott, 1986.
58. Hoy EA, Bill JM, Sykes DH. Very low birthweight: a long-term developmental impairment? *Int J Behav Dev* 1988;11:37.
59. Rose SA. Differential rates of visual information processing in full-term and preterm infants. *Child Dev* 1983;54:1189.
60. Ruff HA, McCarton C, Kurtzberg D, et al. Preterm infants' manipulative exploration of objects. *Child Dev* 1984;55:1166.
61. Drillien CM. *The growth and development of the prematurely born infant*. Edinburgh: Livingstone, 1964.
62. Wiener G, Rider RV, Oppel WC, et al. Correlates of low birthweight: psychological status at eight to ten years of age. *Pediatr Res* 1968; 2:110.
63. Hunt JV, Cooper BAB, Tooley WH. Very low birthweight infants at 8 and 11 years of age: role of neonatal illness and family status. *Pediatrics* 1988;82:596.
64. Halsey CL, Collin MF, Anderson CL. Extremely low birth weight children and their peers: A comparison of preschool performance. *Pediatrics* 1993;91:807.
65. Breslau N, DelDotto JE, Brown GG, et al. A gradient relationship between low birth weight and IQ at age 6 years. *Arch Pediatr Adolesc Med* 1994;148:377.
66. Zarin-Ackerman J, Lewis M, Driscoll JM. Language development in 2-year-old normal and risk infants. *Pediatrics* 1977;59:982.
67. Largo RH, Molinari L, Comenale-Pinto L, et al. Language development of term and preterm children during the first five years of life. *Dev Med Child Neurol* 1986;28:333.
68. Michelsson K, Noronen M. Neurological, psychological and articulatory impairment in fiveyearold children with a birthweight of 2000 g or less. *Eur J Pediatr* 1983;137:96.
69. Hubatch LM, Johnson CJ, Kistler DJ, et al. Early language abilities of high-risk infants. *J Speech Hear Disord* 1985;50:195.
70. Bennett FC, Robinson NM, Sells CJ. Hyaline membrane disease, birthweight, and gestational age: effects on development in the first two years. *Am J Dis Child* 1982;136:888.
71. Drillien CM. Abnormal neurologic signs in the first year of life in low birthweight infants: possible prognostic significance. *Dev Med Child Neurol* 1972;14:575.
72. Amiel-Tison C. A method for neurologic evaluation within the first year of life. *Curr Prob Pediatr* 1976;7:1.
73. Coolman RB, Bennett FC, Sells CJ, et al. Neuromotor development of graduates of the neonatal intensive care unit: patterns encountered in the first two years of life. *J Dev Behav Pediatr* 1985;6:327.
74. Drillien CM, Thomson AJM, Burgoyne K. Low birthweight children at early school age: a longitudinal study. *Dev Med Child Neurol* 1980;22:26.
75. Ross G, Lipper EG, Auld PAM. Consistency and change in the development of premature infants weighing less than 1501 grams at birth. *Pediatrics* 1985;76:885.
76. Burns YR, Bullock ML. Comparison of abilities of preterm and mature born children at 5 years of age. *Aust Paediatr J* 1985;21:31.
77. Crowe TK, Deitz JC, Bennett FC, et al. Preschool motor skills of children born prematurely and not diagnosed as having cerebral palsy. *J Dev Behav Pediatr* 1988;9:189.
78. Ferrari F, Grosoli MV, Fontana G, et al. Neurobehavioral comparison

of low-risk preterm and full-term infants at term conceptional age. *Dev Med Child Neurol* 1983;25:450.
79. Freidman SL, Jacobs BS, Werthmann MW. Preterms of low medical risk: spontaneous behaviors and soothability at expected date of birth. *Infant Behav Dev* 1982;5:3.
80. Aylward GP, Hatcher RP, Leavitt LA, et al. Factors affecting neurobehavioral responses of preterm infants at term conceptional age. *Child Dev* 1984;55:1155.
81. Kurtzberg D, Hilpert PL, Kreuzer JA, et al. Differential maturation of cortical auditory evoked potentials to speech sounds in normal full-term and very low birthweight infants. *Dev Med Child Neurol* 1984;26:466.
82. Anders TF, Keener M. Developmental coarse of nighttime sleep–wake patterns in full-term and premature infants during the first year of life: I. *Sleep* 1985;8:173.
83. Fox NA, Porges SW. The relation between neonatal heart period patterns and developmental outcome. *Child Dev* 1985;56:28.
84. Kaga K, Hashira S, Marsh RR. Auditory brainstem responses and behavioral responses in preterm infants. *Br J Audiol* 1986;20:121.
85. Anders TF, Keener M, Kraemer H. Sleep–wake state organization, neonatal assessment and development in premature infants during the first year of life: II. *Sleep* 1985;8:193.
86. Cohen SE, Parmelee AH, Beckwith L, et al. Cognitive development in preterm infants: birth to eight years. *J Dev Behav* Pediatr 1986;7:102.
87. DiVitto B, Goldberg S. The effects of newborn medical status on early parent–infant interactions. In Field TM, ed. *Infants born at risk.* New York: Spectrum, 1979:311.
88. Field TM. Interaction patterns of preterm and term infants. In Field TM, ed. *Infants born at risk.* New York: Spectrum, 1979:333.
89. Watt J. Interaction and development in the first year: I. The effects of prematurity. *Early Hum Dev* 1986;13:195.
90. Field TM. High-risk infants "have less fun" during early interactions. *Top Early Child Spec Educ* 1983;3(1):77.
91. Crnic KA, Ragozin AS, Greenberg MT, et al. Social interaction and developmental competence of preterm and full-term infants during the first year of life. *Child Dev* 1983;54:1199.
92. Malatesta CZ, Grigoryev P, Lamb C, et al. Emotion socialization and expressive development in preterm and full-term infants. *Child Dev* 1986;57:316.
93. Kopp CB. Risk factors in development. In Haith MM, Campos JJ, eds. *Handbook of child psychology,* vol 2. *Infancy and developmental psychobiology.* New York: John Wiley & Sons, 1983:1081.
94. Dunn HG, Crichton JU, Grunau RVE, et al. Neurological, psychological and educational sequelae of low birthweight. *Brain Dev* 1980;2:57.
95. Dunn HG, ed. Sequelae of low birthweight: the Vancouver Study. *Clin Dev Med* 1986;95:96.
96. Wright FH, Blough RR, Chamberlin A, et al. A controlled follow-up study of small prematures born from 1952 through 1956. *Am J Dis Child* 1972;124:506.
97. Caputo DV, Goldstein KM, Taub HB. The development of prematurely born children through middle childhood. In Field TM, ed. *Infants born at risk.* New York: Spectrum, 1979:219.
98. Nickel RE, Bennett FC, Lamson FN. School performance of children with birthweights of 1000 g or less. *Am J Dis Child* 1982;136:105.
99. Klein NK, Hack M, Breslau N. Children who were very low birthweight: development and academic achievement at nine years of age. *J Dev Behav Pediatr* 1989;10:32.
100. Ross G, Lipper EG, Auld PAM. Educational status and schoolrelated abilities of very low birthweight premature children. *Pediatrics* 1991; 88:1125.
101. Klebanov PK, Brooks-Gunn J, McCormick MC. School achievement and failure in very low birth weight children. *J Dev Behav Pediatr* 1994;15:248.
102. Halsey CL, Collin MF, Anderson CL. Extremely low-birth-weight children and their peers: A comparison of school-age outcomes. *Arch Pediatr Adolesc Med* 1996;150:790.
103. Hall A, McLeod A, Counsell C, et al. School attainment, cognitive ability and motor function in a total Scottish very-low-birthweight population at eight years: A controlled study. *Dev Med Child Neurol* 1995;37:1037.
104. Escalona SK. Babies at double hazard: early development of infants at biologic and social risk. *Pediatrics* 1982;70:670.
105. Breslau N, Klein N, Allen L. Very low birthweight: behavioral sequelae at nine years of age. *J Am Acad Child Adolesc Psychiatry* 1988;27: 605.
106. Klebanov PK, Brooks-Gunn J, McCormick MC. Classroom behavior of very low birth weight elementary school children. *Pediatrics* 1994; 94:700.
107. Allen MC. Developmental outcome and follow-up of the small for gestational age infant. *Semin Perinatol* 1984;8:123.
108. Fitzhardinge PM, Stevens EM. The small-for-date infant: II. Neurological and intellectual sequelae. *Pediatrics* 1972;50:50.
109. Westwood M, Kramer MS, Munz D, et al. Growth and development of full-term nonasphyxiated small-for-gestational-age newborns: follow-up through adolescence. *Pediatrics* 1983;71:376.
110. Neligan GA, Kolvin I, Scott DM, et al. Born too soon or born too small: a follow-up study to seven years of age. *Clin Dev Med* 1976;61:81.
111. Commey JO, Fitzhardinge PM. Handicap in the preterm small-for-gestational-age infant. *J Pediatr* 1979;94:779.
112. Drillien CM. Aetiology and outcome in low birthweight infants. *Dev Med Child Neurol* 1972;14:563.
113. McCarton CM, Wallace IF, Divon M, et al. Cognitive and neurologic development of the premature, small for gestational age infant through age 6: Comparison by birth weight and gestational age. *Pediatrics* 1996;98:1167.
114. Shaywitz BA. The sequelae of hypoxicischemic encephalopathy. *Semin Perinatol* 1987;11:180.
115. Volpe JJ. Perinatal hypoxicischemic brain injury. *Pediatr Clin North Am* 1976;23:383.
116. Paneth N, Stark RI. Cerebral palsy and mental retardation in relation to indicators of perinatal asphyxia: an epidemiologic overview. *Am J Obstet Gynecol* 1983;147:960.
117. Apgar V, James LS. Further observations on the newborn scoring system. *Am J Dis Child* 1962;104:419.
118. Hegyi T, Carbone T, Anwar M, et al. The Apgar score and its components in the preterm infant. *Pediatrics* 1998;101:77.
119. Nelson KB, Ellenberg JH. Apgar scores as predictors of chronic neurologic disability. *Pediatrics* 1981;68:36.
120. Freeman JM, Nelson KB. Intrapartum asphyxia and cerebral palsy. *Pediatrics* 1988;82:240.
121. Sarnat HB, Sarnat MS. Neonatal encephalopathy following fetal distress: a clinical and electroencephalographic study. *Arch Neurol* 1976; 33:696.
122. Finer NN, Robertson CM, Richards RT, et al. Hypoxicischemic encephalopathy in term neonates: perinatal factors and outcome. *J Pediatr* 1981;98:112.
123. Fitzhardinge PM, Flodmark O, Fitz CR, et al. The prognostic value of computed tomography as an adjunct to assessment of the term infant with postasphyxial encephalopathy. *J Pediatr* 1981;99:777.
124. Byrne P, Welch R, Johnson MA, et al. Serial magnetic resonance imaging in neonatal hypoxicischemic encephalopathy. *J Pediatr* 1990; 117:694.
125. Robertson CM, Finer NN, Grace MG. School performance of survivors of neonatal encephalopathy associated with birth asphyxia at term. *J Pediatr* 1989;114:753.