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NEUROLOGIC AND DEVELOPMENTAL DISABILITY AFTER EXTREMELY PRETERM BIRTH

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ABSTRACT

Background Small studies show that many children born as extremely preterm infants have neurologic and developmental disabilities. We evaluated all children who were born at 25 or fewer completed weeks of gestation in the United Kingdom and Ireland from March through December 1995 at the time when they reached a median age of 30 months.

Methods Each child underwent a formal assessment by an independent examiner. Development was evaluated with use of the Bayley Scales of Infant Development, and neurologic function was assessed by a standardized examination. Disability and severe disability were defined by predetermined criteria.

Results At a median age of 30 months, corrected for gestational age, 283 (92 percent) of the 308 surviving children were formally assessed. The mean (\pm SD) scores on the Bayley Mental and Psychomotor Developmental Indexes, referenced to a population mean of 100, were 84 ± 12 and 87 ± 13 , respectively. Fifty-three children (19 percent) had severely delayed development (with scores more than 3 SD below the mean), and a further 32 children (11 percent) had scores from 2 SD to 3 SD below the mean. Twenty-eight children (10 percent) had severe neuromotor disability, 7 (2 percent) were blind or perceived light only, and 8 (3 percent) had hearing loss that was uncorrectable or required hearing aids. Overall, 138 children had disability (49 percent; 95 percent confidence interval, 43 to 55 percent), including 64 who met the criteria for severe disability (23 percent; 95 percent confidence interval, 18 to 28 percent). When data from 17 assessments by local pediatricians were included, 155 of the 314 infants discharged (49 percent) had no disability.

Conclusions Severe disability is common among children born as extremely preterm infants and remains a major challenge in this group of children. (N Engl J Med 2000;343:378-84.)

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MOST studies that describe the outcome of premature infants are based on birth weight and thus confound the effects of extremely preterm birth with those of intrauterine growth restriction.¹ However, physicians and parents contemplating the prognosis of extremely preterm infants require reliable information based on gestational age with which to plan care around the time of birth and thereafter.^{2,3} Information from individual hospitals has been collected from small numbers of infants over a long time and therefore includes data on infants treated in many different ways.

To collect information relevant to modern perinatal care, we conducted a prospective study of all infants born at 20 through 25 completed weeks of gestation in the United Kingdom and Ireland during a 10-month period beginning in March 1995. We obtained information on clinical findings and hospital outcome for all of the 811 extremely preterm infants born during this period who were admitted to neonatal intensive care units and discharged home.⁴

Disability is common among extremely premature infants who survive,⁵ but there are few population-based studies of the development of these infants.⁶⁻⁹ Here we report the results of a neurologic and developmental assessment performed a median of 30 months after the expected date of delivery in the survivors of the study cohort.

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METHODS

Study Subjects

We identified all infants born at 20 through 25 weeks of gestation (as determined by the date of the mother's last menstrual period and by early ultrasonography) in all 276 maternity units in the United Kingdom and Ireland from March through December 1995. Of the 4004 infants identified, 1185 had signs of life at birth, and 843 of these were admitted to neonatal intensive care units (the remainder died in the delivery room) (Table 1). For these 843 infants, gestation was recalculated by using the date of the last menstrual period, by review of ultrasound studies done before 20 weeks, or (in the case of 29 infants) on the basis of clinical examination by a pediatrician. Three of these 29 infants were considered by the pediatrician to have been born at 26 weeks or more of gestation and were therefore excluded. If the estimates based on the last menstrual period and on ultrasonography were both available and were discrepant by at least 14 days, the ultrasound estimate was used; this resulted in the exclusion of an additional 29 infants. Thus, there remained 811 infants admitted to the neonatal intensive care unit whose gestational age was not more than 25 weeks and 6 days. Of these, 497 died in the hospital and 314 were discharged home. Six infants died after discharge, and six left the United Kingdom or Ireland.

Between January 1998 and January 1999, the parents of the 302 survivors living in the United Kingdom or Ireland were offered the opportunity to have their children undergo a standardized follow-up assessment. The parents of 16 children declined the invitation, and the parents of 3 others failed to bring their children for their prearranged evaluation; thus 283 of the survivors (92 percent) participated in this study. Of the 25 surviving children who did not take part, information was available on 17 from assessments performed by their local pediatricians at about 30 months of age corrected for gestation, and on a further 6 from assessments performed locally at about 12 months of corrected age. The data obtained were sufficient to allow us to determine whether the child had a disability. Of these 23 children, 9 were classified as severely disabled, 4 as having other disabilities, and 10 as having no disability. Information on outcome was therefore unavailable for only 2 of 308 surviving children.

The study was approved by each local research ethics commit-

tee before collection of the original data. All families for whom outcome is reported gave written informed consent for the examination.

Assessment

Each child was examined in a hospital outpatient clinic or health center near the family home (235 children) or at home (48 children). The assessment consisted of a detailed medical history obtained from a semistructured interview with the family; a clinical examination, including neurologic assessment¹⁰; a classification of the degree and type of disability^{11,12}; a functional classification of hearing and visual ability¹²; and a growth assessment, including measurement of maximal occipitofrontal head circumference with a LASSO-O tape (Child Growth Foundation, London). Development was assessed with use of the Bayley Scales of Infant Development (second edition),¹³ which yielded scores for mental and psychomotor development with a standardization mean of 100 and standard deviation of 15 points. Scores over 100 indicated advanced development for age. Development was considered severely impaired if the scores were less than 55, moderately impaired if they were 55 to 69, and mildly impaired if they were 70 to 84. There are no standardization data for children in the United Kingdom, but in a study of 850 three-year-olds in the Avon region of the United Kingdom, most of whom were born at term, the mean mental development score was 99.3 ± 11.3 (SD) and the mean psychomotor development score was 96.0 ± 14.7 (unpublished data). We used the U.S. standardization norms,¹³ with a mean of 100 and a standard deviation of 15. Scores were corrected for gestational age because, even at this age, uncorrected results would alter performance by 12.5 to 15.0 percent. If the child was unable to complete the Bayley assessment (because of poor vision, for example), the pediatrician estimated the child's developmental level as severely or moderately impaired (equivalent to Bayley scores under 55 or 55 to 69, respectively) or as not impaired.

Developmental Panel

Ten experienced developmental pediatricians were recruited to perform the assessments. All attended a course in which they were trained in all aspects of the assessments. A psychologist provided instruction in the use of the Bayley scales. After the training course, all the pediatricians submitted video recordings of pilot Bayley as-

TABLE 1. SUMMARY OF OUTCOMES AMONG INFANTS BORN ALIVE AT 22 THROUGH 25 WEEKS OF GESTATION.*

OUTCOME	22 Wk	23 Wk	24 Wk	25 Wk
	(N=138)	(N=241)	(N=382)	(N=424)
	number (percent)			
Died in delivery room	116 (84)	110 (46)	84 (22)	67 (16)
Admitted to NICU	22 (16)	131 (54)	298 (78)	357 (84)
Died in NICU	20 (14)	105 (44)	198 (52)	171 (40)
Survived to discharge	2 (1)	26 (11)	100 (26)	186 (44)
Died after discharge	0	1 (0.4)	2 (0.5)	3 (0.7)
Lost to follow-up	0	0	1 (0.3)	1 (0.2)
Had severe disability at 30 mo	1 (0.7)	8 (3)	24 (6)	40 (9)
Had other disabilities at 30 mo	0	6 (2)	28 (7)	44 (10)
Survived without overall disability at 30 mo				
As a percentage of live births	1 (0.7)	11 (5)	45 (12)	98 (23)
As a percentage of NICU admissions	1 (5)	11 (8)	45 (15)	98 (27)

*NICU denotes neonatal intensive care unit. Three infants, all of whom died, were admitted at less than 22 weeks of gestational age. For infants who died in the delivery room, gestational age was based on the estimate used in the delivery room. For infants who were admitted to the NICU, gestational age was confirmed postnatally.

assessments, which were scored independently. All the pediatricians reached a prespecified level of agreement of more than 80 percent with the psychologist for individual items on the Bayley scales before study testing commenced. Further tapes were submitted at random during the study, and scoring was rechecked. Overall agreement was reached on 91 percent of the items making up the Mental Development Index and 88 percent of the items of the Psychomotor Development Index. One pediatrician left during the study and was replaced by another, who achieved similar levels of agreement for the Bayley assessment. The developmental pediatricians were unaware of the neonatal courses of the children they evaluated.

Classification of Disability

Disability was classified according to a previously published scheme.¹¹ A “severe disability” was defined as one that was likely to put the child in need of physical assistance to perform daily activities. Disabilities that did not fall into this category were referred to simply as “other disabilities.” The criteria for severe and other disabilities in each neurologic domain are shown in Table 2. Cerebral palsy was classified retrospectively according to the descriptions of function for each limb¹² in children with abnormal results on neurologic examination.¹⁰ The categories were diplegia, in which upper-limb function was better than lower-limb function, despite asymmetries; hemiplegia, in which lower-limb function was better

than upper-limb function, usually with asymmetry; quadriplegia, in which all four limbs appeared equally affected; and other, non-spastic types of cerebral palsy, such as hypotonia and dyskinesia. This classification was independent of the degree of disability.

Statistical Analysis

Data collected on standardized forms and Bayley records were sent by mail to the study center, where they were encoded for computer analysis with SPSS for Windows software (release 8.0.0, SPSS, Chicago). To check for accuracy, the data were double-entered and the files were compared. The data for each infant were examined and outliers were verified before the data were combined with the main study data set for analysis. Categorical outcomes were compared with use of chi-square tests for trends, as appropriate, or Fisher’s exact test. Continuous outcomes were compared with use of independent Student’s t-tests. All statistical tests were two-sided.

RESULTS

The outcome at 30 months of age is summarized in Figure 1, which is based on the 314 children discharged home and includes all the information available on the 25 children (8 percent) who were not assessed or who were abroad. Table 1 uses these data to show the outcome for the whole study cohort summarized according to gestational age, with the number of live births as the denominator. Two hundred eighty-three children were formally assessed at a median corrected age of 30 months (range, 28 to 40); 90 percent of the assessments occurred between 29 and 32 months.

Bayley Assessments

At least one of the two Bayley indexes could be completed for 251 of the 283 infants (89 percent). The mean score on the Mental Development Index was 84±12, and the score on the Psychomotor Development Index was 87±13. The range of scores according to test scale and gestational age is shown in Figure 2.

On the basis of the lower of the scores on the Mental and Psychomotor Development Indexes, and including the estimated scores of those who were unable to complete the assessment, 53 children (19 percent; 95 percent confidence interval, 14 to 24 percent) had scores more than 3 SD below the mean. These children were classified as severely disabled.¹¹ The scores were from 2 SD to 3 SD below the mean (indicating moderately delayed development) in 32 children (11 percent; 95 percent confidence interval, 9 to 17 percent). These children were assigned to the “other disability” category. The variation in Bayley scores according to gestational age, sex, and single or multiple birth is shown in Table 3. The scores did not vary substantially with gestational age or multiple as compared with single birth, but boys had significantly lower psychomotor scores than girls (mean difference, 5.7; 95 percent confidence interval, 1.9 to 8.6).

Neuromotor Function

Overall, 28 children had severe disabilities of neuromotor function (10 percent; 95 percent confidence

TABLE 2. NEUROLOGIC FUNCTION AT 30 MONTHS IN 283 CHILDREN BORN AT 22 THROUGH 25 WEEKS OF GESTATION.

CRITERIA FOR DISABILITY*	No.	PERCENT (95% CI)†
Neuromotor domain		
Gait		
Nonfluent gait	33	12 (8–16)
Abnormal gait, reduced mobility	6	2 (1–5)
Unable to walk without assistance	27	10 (6–14)
Sitting		
Sits unsupported but unstable	7	2 (1–5)
Sits supported	6	2 (1–5)
Unable to sit	8	3 (1–6)
Hand use		
Some difficulty feeding with both hands	26	9 (6–13)
Unable to use hands to feed self	12	4 (2–7)
Head control		
Unstable, but no support required	6	2 (1–5)
Unable to control head movement without support	3	1 (0.2–3)
No head control	0	—
Sensory and communication domains		
Vision		
Normal with correction	17	6 (4–10)
Useful vision but not fully correctable	28	10 (7–14)
Blind or perceives light only	7	2 (1–5)
Hearing		
Impaired, hearing aid not used	33	12 (8–16)
Impaired, corrected with hearing aid	3	1 (0.2–3)
Impaired, uncorrected even with hearing aid	5	2 (1–4)
Communication		
Delay in communicating by speech‡	64	23 (18–28)
Delay in speech and other systematized method of communicating	13	5 (2–8)
Communicating by systematized method only	3	1 (0.2–3)
Not communicating by speech or other method	15	5 (3–9)
Recurrent nonfebrile seizures	17	6 (3–10)
Ventriculoperitoneal shunt‡	12	4 (3–8)

*The criteria for severe disability are in boldface type.
 †CI denotes confidence interval.
 ‡Children with the condition were not included in “other disability” group.

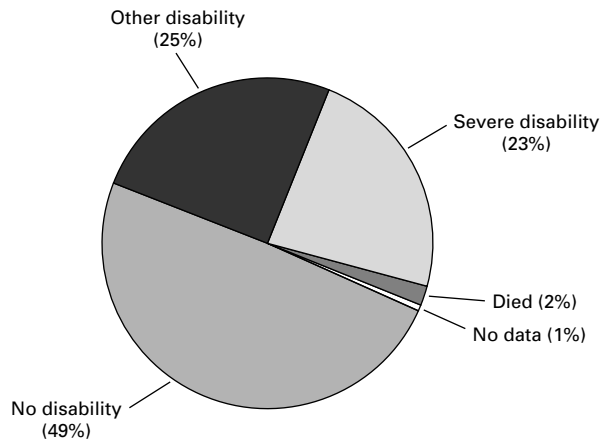


Figure 1. Summary of Outcome with Respect to Overall Disability at 30 Months for 314 Children Born at 22 through 25 Weeks of Gestation.

interval, 7 to 14 percent), and 39 children had other neuromotor disabilities (14 percent; 95 percent confidence interval, 10 to 18 percent) (Table 3). Of these 67 children, 50 had a recognizable pattern of cerebral palsy (18 percent of the study cohort). The degree of disability in children with each type of cerebral palsy is

shown in Table 4. Of the children with cerebral palsy, 27 had severe disability (54 percent). Boys were more likely to have cerebral palsy than girls ($P=0.009$), but there were no differences related to either gestational age or multiple as compared with single birth.

Sensory Morbidity and Communication Difficulties

Seven children were blind or could see only light; six of these children had received treatment for retinopathy of prematurity (Table 2). Many children had other, less severe, visual impairments: squint was present in 71 (25 percent), and 28 (10 percent) wore eyeglasses. Five children had profound hearing loss that could not be corrected with hearing aids, and a further 36 had lesser degrees of hearing loss. In 18 children there was no recognizable speech at 30 months of age; hearing was normal in 15 of these children.

Severe Disability

Severe disability in the developmental, neuromotor, or sensory and communication domains was present in 64 children (23 percent). Twenty-nine children had disabilities in more than one of the three domains, including 13 with disabilities in each domain. Twenty-seven (10 percent) were classified as having a severe disability on the basis of poor developmental progress without severe neuromotor or sensory and commu-

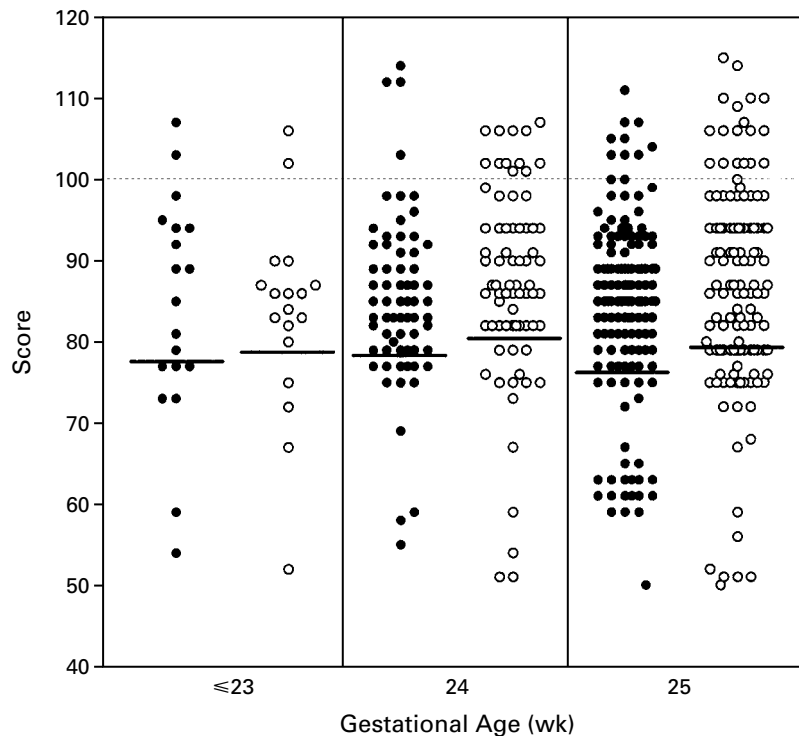


Figure 2. Individual Scores on the Bayley Scales at 30 Months According to Gestational Age. Scores on the Mental Development Index (231 infants) are indicated by solid circles, and scores on the Psychomotor Development Index (225 infants) by open circles. The horizontal lines represent means.

TABLE 3. DEVELOPMENTAL SCORES AND DEGREE AND TYPE OF DISABILITY AT 30 MONTHS ACCORDING TO GESTATIONAL AGE, SEX, AND FREQUENCY OF MULTIPLE BIRTH AMONG CHILDREN BORN AT 22 THROUGH 25 WEEKS OF GESTATION.*

VARIABLE	GESTATIONAL AGE			SEX		BIRTH		TOTAL
	≤23 WK	24 WK	25 WK	FEMALE	MALE	SINGLE	MULTIPLE	
Bayley score								
Mental development								
No. of children	19	69	143	133	98	169	62	231
Score	84±14	85±11	84±12	85±11	83±12	84±12	85±11	84±12
Psychomotor development								
No. of children	19	74	132	129	96	166	59	225
Score	85±15	87±12	87±13	89±12	84±13†	86±13	88±11	87±13
Categorization according to domain								
No. of children	26	90	167	152	131	207	76	283
Development — no. (%)‡								
No disability (scores >85)	11 (42)	27 (30)	65 (39)	67 (44)	36 (27)	73 (35)	30 (39)	103 (36)
Mild disability (scores 70–84)	8 (31)	36 (40)	51 (31)	54 (36)	41 (31)	67 (32)	28 (37)	95 (34)
Moderate disability (scores 55–69)	0	10 (11)	22 (13)	13 (9)	19 (15)	25 (12)	7 (9)	32 (11)
Severe disability (scores ≤54)	7 (27)	17 (19)	29 (17)	18 (12)	35 (27)§	42 (20)	11 (14)	53 (19)
Neuromotor function — no. (%)								
No disability	22 (85)	67 (74)	127 (76)	127 (84)	89 (68)	155 (75)	61 (80)	216 (76)
Severe disability	2 (8)	11 (12)	15 (9)	10 (7)	18 (14)¶	19 (9)	9 (12)	28 (10)
Other disability	2 (8)	12 (13)	25 (15)	15 (10)	24 (18)	33 (16)	6 (8)	39 (14)
Disabilities of hearing, vision, or communication — no. (%)								
No disability	15 (58)	58 (64)	115 (69)	103 (68)	85 (65)	147 (71)	41 (54)	188 (66)
Severe disability	3 (12)	10 (11)	12 (7)	12 (8)	13 (10)	16 (8)	9 (12)	25 (9)
Other disability	8 (31)	22 (24)	40 (24)	37 (24)	33 (25)	44 (21)	26 (34)	70 (25)

*Plus–minus values are means ±SD; scores for those who did not attain the minimal index score of 50 were excluded from the calculation of the standard deviation.

†P=0.002 by the independent t-test.

‡Development was assessed with use of the Bayley Scales of Infant Development.

§P<0.001 by the chi-square test for trend.

¶P=0.003 by the chi-square test for trend.

||P=0.02 by the chi-square test for trend.

TABLE 4. DISABILITY AND DISTRIBUTION OF CLINICAL SIGNS OF CEREBRAL PALSY AMONG 50 30-MONTH-OLD CHILDREN WHO WERE BORN AT 22 THROUGH 25 WEEKS OF GESTATION.

SIGN	SEVERE DISABILITY	OTHER DISABILITY	TOTAL
		no. (%)	
Diplegia	12 (44)	15 (56)	27
Hemiplegia	1 (20)	4 (80)	5
Quadriplegia	11 (92)	1 (8)	12
Other	3 (50)	3 (50)	6

nication problems (only six of these children had no other disability), seven had severe disability in the sensory and communication domain (three of these had other disabilities), and two had severe neuromotor disabilities without severe disability in other domains (both children had quadriplegia).

Head Growth

Head circumference was measured in 278 children (98 percent) and related to United Kingdom population norms. Overall, the mean head circumference was 1.6 SD below the mean for corrected age. Similarly, head circumference was lower in those with any severe disability than in those with no disability (P<0.001). Among 155 children with no disability, 37 (24 percent) had a head circumference more than 2 SD below the mean.

DISCUSSION

In this large cohort of extremely preterm infants, we found that disability in the domain of mental and psychomotor development, neuromotor function, or sensory and communication function was present in about half of all survivors at 30 months of corrected age, with approximately one quarter meeting the criteria for severe disability. There was no relation between the pattern of morbidity and either gestational age or the presence of multiple birth, but boys were more likely to be disabled than girls. This morbidity must be viewed in the context of mortality in

this particularly vulnerable group. We chose live births, rather than total births, as our denominator because infants who are stillborn after therapeutic termination of the pregnancy are included among total births (unpublished data). In a study such as this, with data from a large number of centers of various sizes and staffing structures and inevitable differences of approach to the birth of an extremely preterm infant, we could neither standardize nor validate definitions of resuscitation attempts; thus, the delivery-room treatment of those reported to show signs of life but not admitted to the neonatal intensive care unit was not recorded. It is a matter of conjecture whether a more aggressive universal policy of resuscitation would have altered these outcomes.

The strengths of this study lie in the fact that the cohort was drawn prospectively from an entire population over a short period, resulting in findings relevant to current neonatal practice in the United Kingdom and Ireland. Formal assessment data were available on nearly all survivors, and the assessments were performed by independent examiners unaware of the children's neonatal history. We examined the children at 30 months, but we recognize that some neurologic disabilities may continue to evolve, and assessment at 5 years would probably result in a more accurate measure of final neurologic outcome.¹⁴⁻¹⁶ We chose to continue correcting for prematurity beyond the normally accepted age of two years because of the magnitude of the deficits in this particular group. Had we not used corrected age, the mean developmental scores would have been even lower, but the children with severe developmental delay would nonetheless have been identified.¹⁷

The majority of previous studies of extremely preterm infants have reported outcome according to birth-weight categories, and few have reported outcome according to gestational age. Reporting according to birth-weight categories often leads to the inclusion of infants who are gestationally more mature but whose growth was restricted, in addition to those with appropriate growth for their gestational ages. The inclusion of these more mature, growth-restricted infants confers an artificial neurodevelopmental advantage on such a group as compared with a group made up of infants with appropriate growth.^{18,19} In the current published literature, rates of severe disability vary between 18 and 40 percent for those born at 25 weeks of gestation or later.⁵ Much of this variation in outcome may be attributable to small samples, use of cohorts from tertiary referral centers rather than geographic regions, differing proportions of infants born in or outside the hospital, high rates of loss to follow-up, and the inconsistent classification of disability.

The Victorian Infant Collaborative Study Group presented data from a cohort of 220 infants born in the state of Victoria, Australia, at 27 or fewer weeks

of gestation during 1991 and 1992 and who were assessed at two years of age.⁹ The Mental Development Index of the original Bayley Scales was used, and the results were expressed as standardized normal quotients calculated on the basis of the means and standard deviations of scores of normal-birth-weight infants. Severe disability — defined as one or more mental development scores 3 SD or more below the mean, cerebral palsy such that the child was unlikely ever to walk, or bilateral blindness — was present in 9 percent (95 percent confidence interval, 4 to 18 percent) of those who were born at 25 or fewer weeks of gestation.

This percentage appears considerably less than the 23 percent in our cohort. If we reclassify our cohort according to the above definition, then 15 percent of the children (95 percent confidence interval, 11 to 20 percent) would be labeled as severely disabled. This classification fails to consider the important additional severe disability imposed by functional disorders of the proximal axial musculature and arms, severe psychomotor delay, and deafness or communication problems. In contrast to our study findings, the Australian study found that the proportion of infants with disability increased with decreasing gestational age.

The United Kingdom Northern Neonatal Network collected prospective population-based outcome data between 1983 and 1994 on 580 infants born at 27 weeks or less of gestational age.⁸ The cohort was assessed at one year, and a more detailed assessment of development, based on the Griffiths Scales of Mental Development,²⁰ was performed at two years for those born in 1983, 1987, and 1991. Disability was defined by the same criteria as in this study.¹¹ At one year, severe disability was found in 24 percent of the infants born at 25 weeks or less of gestation. At two years, none of the nine survivors of those born at 25 weeks or less of gestation had severe disability that was likely to prevent independent living; in contrast, severe disability was present in 10 percent of those born at 25 through 27 weeks of gestation. In agreement with our findings, the investigators found that boys were significantly more likely to be disabled.

Cerebral palsy is often chosen as an index of long-term outcome by which changes in neonatal and perinatal care can be measured, because the clinical syndromes are often recognizable by two years of age. However, as a means of identifying disability, this method would lead to an underestimation of motor disability in the children in our study: of 67 with abnormal motor function, only 50 (75 percent) had a recognizable pattern of cerebral palsy.

The comprehensive nature of our study allowed us to provide outcome data for virtually all live births at 25 completed weeks or less of gestation in a whole population. This information is important for obstetricians, midwives, and pediatricians to use in discus-

sions with parents. It provides a background to facilitate decision making and eliminates the bias inherent in center-based studies, which may be misleading because of wide confidence intervals and selective referral of mothers and infants.

Our study documents the outcome of extremely preterm infants at 30 months of corrected age; our data can provide information concerning only the most severe disabilities. Infants born extremely preterm are also at risk for later behavioral,^{21,22} fine-motor,^{23,24} and educational^{25,26} difficulties. The place of intervention early after discharge to increase developmental performance is still unclear,²⁷ and the benefits of such intervention may be only minimal in the short term.²⁸ The prevention or amelioration of disability in survivors of extreme prematurity remains one of the most important challenges in medicine.

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APPENDIX

Members of the EPICure Study Group are as follows: Developmental Panel — A.J. Bennett, M.J. Cruwys, M.C. Dick, S. Egan, A.F. Livingstone, L.J. Logie, R.H. MacGregor, B. Mallya, M.X. Poblete, J.F. Schulte, N.S. Wood, C. Lawson (psychologist), H. Palmer (administrator), and E.M. Hennessy (statistician); Steering Group — P.J. Steer (Chair; London), K. Costeloe (London), A.T. Gibson (Sheffield), I.A. Laing (Edinburgh), M.J. Lewins (Lincoln), N. Marlow (Nottingham), P.O.D. Pharoah (Liverpool), and A.R. Wilkinson (Oxford). The EPICure Study Group also includes the pediatricians in 276 maternity units in the United Kingdom and Ireland who contributed data to the study.

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