Comparison of Management Strategies for Extreme Prematurity in New Jersey and the Netherlands: Outcomes and Resource Expenditure

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ABSTRACT. ***Objective.*** **To quantify differences in resource expenditure in the perinatal period and long-term outcome of extremely premature infants who received systematically different approaches to neonatal intensive care.**

Methods. **Perinatal management, mortality, prevalence of disabling cerebral palsy (DCP), and resource expenditure of 2 population-based inception cohorts of extremely premature infants born in the mid-1980s were compared. Electronic fetal monitoring, tocolysis, cesarean section delivery, and assisted ventilation were used to characterize management approaches. Participants included all live births at 23 to 26 weeks' gestation in a 3-county area of central New Jersey (NJ) from 1984 to 1987 (*N* = 146) and throughout the Netherlands (NETH) in 1983 (*N* = 142). Mortality and the prevalence of DCP were the primary outcomes. Numbers of hospital days with and without assisted ventilation were the measures of resource expenditure.**

Results. **Electronic fetal monitoring (100% vs 38%), cesarean section (28% vs 6%), and assisted ventilation (95% vs 64%) were all more commonly used in NJ than in NETH. Ten percent of NJ deaths occurred without assisted ventilation, compared with 45% of Dutch deaths. A total of 1820 ventilator days were expended per 100 live births in NJ, compared with 448 in NETH. The increase in the number of nonventilator days (3174 vs 2265 days per 100 live births) did not reach statistical significance. Survival to age 2 (46 vs 22%) and the prevalence of DCP among survivors (17.2 vs 3.4%) were significantly greater in NJ at age 2 than in NETH at age 5.**

Conclusions. **Near universal initiation of intensive care in NJ, compared with selective initiation of intensive care in NETH, was associated with 24.1 additional survivors per 100 live births, 7.2 additional cases of DCP per 100 live births, and a cost of 1372 additional ventilator days per 100 live births.** ***Pediatrics*** **2001;108:1269–1274; *extreme prematurity, mortality, cerebral palsy, neonatal intensive care.***

ABBREVIATIONS. NETH, the Netherlands; NBH, neonatal brain hemorrhage; NJ, New Jersey; POPS, Project on Preterm and Small for Gestational Age Infants; EFM, electronic fetal monitoring; DCP, disabling cerebral palsy; CP, cerebral palsy; CI, confidence interval.

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Care of the extremely premature newborn in the United States has been more aggressive than in some European countries. Many neonatologists in the United States offer intensive care to all infants considered to have any chance of survival. By contrast, some European neonatologists are more selective in initiating intensive care to the most premature infants because such care is viewed as futile or likely to result in a bleak long-term outcome. Rhoden[1] characterized these approaches to care as the "wait until certain strategy" (treat all potentially viable infants until it is almost certain that they will die) and the "statistical prognostic strategy" (offer treatment only to infants who have or are likely to have reasonably good long-term outcomes). With the latter strategy, some infants die who might have survived without disability, and resources are conserved. With the former strategy, survival is maximized, but resource expenditure and survival with disability are both greater.

Informed decisions about how best to provide care to extremely premature infants require information about survival rates, the prevalence of disabilities among survivors, and resource expenditure with these 2 approaches to care. The purpose of this study was to compare outcomes and neonatal resource expenditures in 2 population-based cohorts of extremely premature infants: 1 from the United States and 1 from the Netherlands (NETH). The cohorts were chosen because they were nearly contemporaneous, they received systematically different approaches to care, and their long-term outcomes have been well-assessed.

METHODS

Participants were drawn from 2 population-based cohorts born in the mid-1980s, which have been described in detail.[2,3] The neonatal brain hemorrhage (NBH) cohort included live births 500 to 2000 g in a 3-county area of central New Jersey (NJ) who were inborn or transferred to 1 of 3 hospitals with neonatal intensive care units from August 27, 1984 to June 30, 1987 (*N* = 1105). The Project on Preterm and Small for Gestational Age Infants (POPS) cohort included live births <1500 g or <32 weeks' gestational age born in NETH between January 1 and December 31, 1983 (*N* = 1338).

As in an earlier review of the literature,[4] 26 completed weeks of gestation was used as the upper bound for extreme prematurity. A lower birth weight limit of 500 g was added in this study because the NBH cohort excluded infants below this threshold. The NJ cohort included 152 live births ≥500 g with recorded gestational ages of 23 to 26 completed weeks, and the NETH cohort included 144 such infants. Review of birth certificates for the 3-county area in NJ showed that the NBH cohort included >94% of all infants 500 to 1000 g born in the 3 counties during the period of the study. Review of the POPS registry, a voluntary obstetric registry (the Landelijke Verloskunde Registratie), and questionnaires completed by Dutch hospitals that did not participate in the POPS study showed that this cohort included 82% of live births ≥500 g and 23 to 26 weeks' gestation born in NETH during 1983. Only 1 (gestational age 26 weeks) of the 32 Dutch births in this birth weight and gestational age range known to not have been enrolled in POPS survived infancy.

Birth weight >99th percentile for gestational age based on Arbuckle et al's[5] growth curves was taken to indicate an incorrect gestational age[6,7]; infants with such birth weights were excluded from the sample. Although these fetal curves were constructed from live births in Canada from 1986 to 1988, the 95th percentile curve is very similar to curves based on data from the United States in 1989[8] and from NETH from 1931 to 1965.[9] However, the latter 2 data sources were not used because the 99th percentile was not available for them. Six of the 152 infants in NJ and 2 of the 144 in NETH group were excluded because birth weight was >99th percentile for gestational age, leaving a final study sample of 146 live births in NJ and 142 live births in NETH.

The prevalences of electronic fetal monitoring (EFM), tocolysis, and cesarean section delivery were used to characterize obstetric management strategy; the prevalence and duration of assisted ventilation were used to characterize neonatal management strategy. Age at discharge home from the neonatal intensive care unit, divided into hospital days on assisted ventilation (ventilator days) and hospital days not on assisted ventilation (nonventilator days), was used as measure of resources expended on neonatal intensive care.[10,11] These data were abstracted from maternal and neonatal records at the time of birth and recorded on standardized reporting forms in each cohort. Survival and prevalence of disabling cerebral palsy (DCP), as defined later in this article, were the outcomes assessed. DCP was chosen as the neurodevelopmental outcome of interest because there has been little variation in its prevalence among industrialized nations,[12] it is related to perinatal factors, it is minimally affected by the social context of the home, and the diagnosis can be made reliably.[13]

In the NBH cohort, gestational age was estimated from prenatal ultrasounds, prenatal and labor and delivery records, and a postnatal maternal interview. Preference was given to consistency across methods of estimation and prenatal ultrasound dating before 20 weeks' gestation, as previously described.[14] In the POPS cohort, gestational age was estimated from last menstrual period, pregnancy testing, and prenatal ultrasound dating. Postnatal examinations were not incorporated into the estimation of gestational age in either cohort.

The diagnosis of cerebral palsy (CP) in the NBH cohort was based on quantitative assessment of motor function at a corrected (for gestation) age of 2 years by a specially trained research nurse or nurse practitioner. Each child's tone, extrapyramidal movements, and deep tendon reflexes in all limbs were scored on ordinal scales. The nurse noted the preservation of primitive reflexes and obtained goniometric measurements of the range of hip abduction and extension, popliteal extension, and ankle dorsiflexion. If the child could not be classified as free of motor disorder, the child was referred to 1 of 4 consultant child neurologists, who determined whether the child had CP. Because not all children referred to a neurologist were seen (by parental choice), medical records were also used. CP was defined a priori to be disabling when, in addition to specific neurologic findings, there was any of the following: inability to walk 10 steps unaided by age 2 years, a Bayley psychomotor developmental index >1 SD below the mental development index, surgical intervention for the motor disorder, or use of braces or other physical assistance devices. In fact, all NJ infants born at 23 to 26 weeks' gestation with DCP had a Bayley psychomotor index of 50 (the assigned minimum). A brief assessment of motor status was also made at 9 years of age by a trained nurse practitioner, who recorded her judgment of probable or definite CP.

Survival in the POPS cohort was based on pediatrician reports at a corrected age of 2 years.[2] (The classification of CP at age 2 in the POPS cohort was based on a report from the child's pediatrician without standardization of criteria.) Motor status was evaluated in the POPS cohort within 6 weeks of the fifth birthday by 1 of 3 specially trained pediatricians using a standardized neurologic assessment during a home visit.[15] The neurologic portion of the assessment evaluated tone, reflexes, and symmetry.[16] Delayed motor development without neurologic abnormalities was classified as gross motor retardation. Abnormalities in tone, reflexes, or symmetry without abnormalities in posture or movement were classified as minor neurologic dysfunction; if there was also abnormal posture or movement, a diagnosis of CP was made. DCP was defined as the inability to walk, eat, or dress independently as the result of neurologic dysfunction with abnormal posture or movements.

The reliability of the DCP diagnosis from the written records of motor findings was assessed in a sample of 50 participants from POPS and 51 participants from NBH. The samples were composed of children without CP, with nondisabling CP, or with DCP in proportions unknown to the reviewers, who were 5 pediatricians experienced in diagnosing CP. The mean kappa score for the distinction of DCP from not DCP for all pairs of reviewers was 0.86 for the NBH sample and 0.88 for the POPS sample.[13]

Continuous variables were compared between groups using the t test for independent samples with or without separate variance estimates, as appropriate, if the data were normally distributed; the Mann–Whitney U test was used if they were not normally distributed. Comparisons between groups at each week of gestational age were made using 2-way analysis of variance. The significance of differences in proportions was calculated by a generalized linear model using an identity link and a binomial error distribution, which allows the inclusion of covariates.

RESULTS

Characteristics of the 2 Populations

Mean gestational age was significantly lower in NJ than in NETH (Table 1), with the distribution more skewed toward 25 and 26 weeks' gestation in NETH than in NJ (Fig 1). As shown in Table 1, no significant differences were found in mean birth weight at each week of gestational age between NJ and NETH, although the prevalence of birth weight <10th percentile for gestational age (Arbuckle et al) among live births in NJ was twice that in NETH. NJ had significantly more black infants than did NETH, and

TABLE 1. Characteristics of Live Births ≥500 g Birth Weight and 23 to 26 Weeks' Gestation

Cohort	New Jersey	The Netherlands	P
Birth year	1984–1987	1983	
Live births	146	142	
Gestational age* (wk)	25.0 ± 0.1	25.4 ± 0.1	<.001
Birth weight* (g)			
23 wk	617 ± 14	693 ± 83	
24 wk	711 ± 23	663 ± 24	.013
25 wk	776 ± 21	839 ± 14	
26 wk	910 ± 21	956 ± 17	
SGA	21 (14%)	10 (7%)	.04
Maternal age* (y)	26.4 ± 0.6	26.7 ± 0.4	.66
PIH/preeclampsia	9 (6%)	3 (2%)	.08
ROM >24 h	41 (31%)	33 (23%)	.17
Chorioamnionitis	12 (8%)	14 (10%)	.63
Male:female	1:0.9	1:0.9	.80
Race			
White	89 (61%)	119 (91%)	
Black	43 (29%)	6 (4%)	<.001
Other	14 (10%)	17 (12%)	
Apgar score‡			
1 min	3 (1–5)	4 (2–6)	.04
5 min	6 (4–7)	6 (2–8)	.88

SGA indicates small for gestational age; PIH, pregnancy-induced hypertension; ROM, rupture of membranes.
* Mean ± SEM.
‡ Median (lower and upper quartiles).

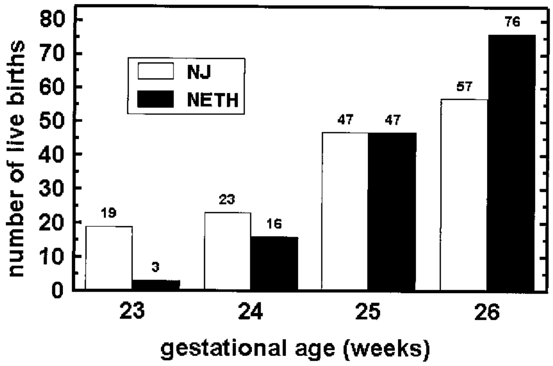

Fig 1. Gestational age distribution within each group ($P < .001$).

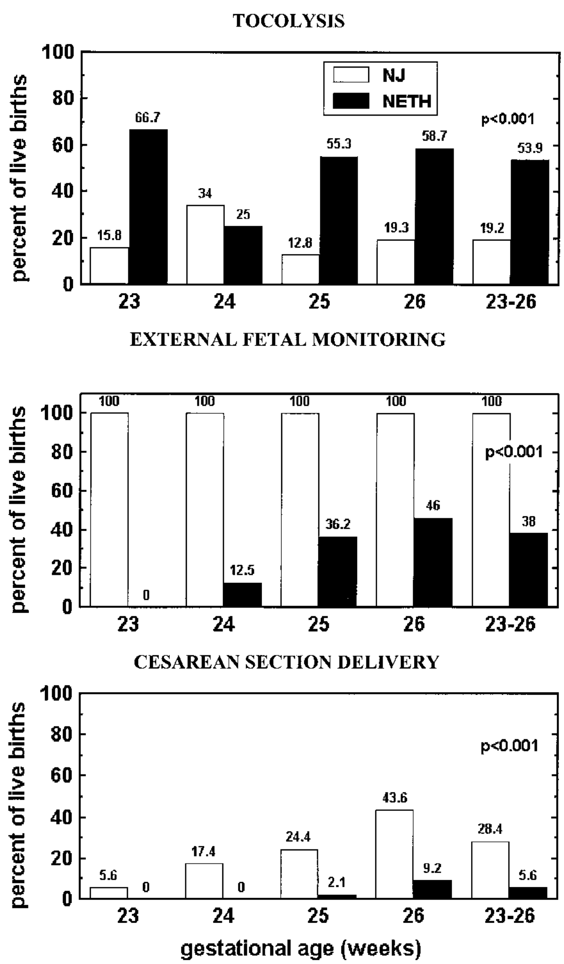

Fig 2. Prevalences of obstetric interventions among live births.

1-minute Apgar scores were significantly lower in NJ than in NETH.

Management Strategies

Much higher prevalences of EFM and cesarean section delivery at each week of gestational age for each group were found in NJ than in NETH (Fig 2). However, tocolysis was more frequently used in NETH.

Assisted ventilation was more commonly used in NJ (95.2 vs 64.1%, $P < .001$). Almost all of this difference resulted from a much more prevalent use of assisted ventilation in infants who subsequently died in NJ (Fig 3). By contrast, all survivors were treated with assisted ventilation in NJ, as were 90.9% in NETH ($P = .07$). Duration of mechanical ventilation was significantly longer in survivors who were ventilated in NJ than in NETH, even when the comparison was limited to infants born at 25 and 26 weeks' gestation (21.3 ± 3.1 vs 11.7 ± 2.0 days, $P = .01$).

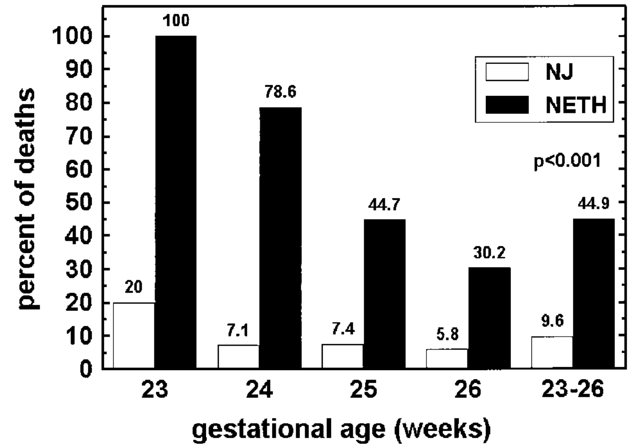

Fig 3. Proportion of in-hospital deaths that occurred without ventilation.

Outcomes

Mortality at 28 days was 45.9% in NJ and 73.2% in NETH ($P < .001$). No infant <25 weeks' gestation survived to 28 days in NETH. Survival to 2 years in NJ was twice that in NETH (Fig 4).

Determination of CP status was available for 58 of 67 (86.6%) NJ survivors and 29 of 31 (93.5%) Dutch survivors ($P = .25$). The prevalence of DCP among survivors was 10 of 58 in NJ and 1 of 29 in NETH. The prevalence of DCP was 5 times greater per 100 survivors and 10 times greater per 100 live births in NJ than in NETH (Fig 5). There were both more survivors without DCP ($P = .005$) and more survivors with DCP ($P = .005$) in NJ than in NETH. The unadjusted risk difference for DCP was 13.8% (95% confidence interval [CI]: 2%–26%; $P = .02$). The risk

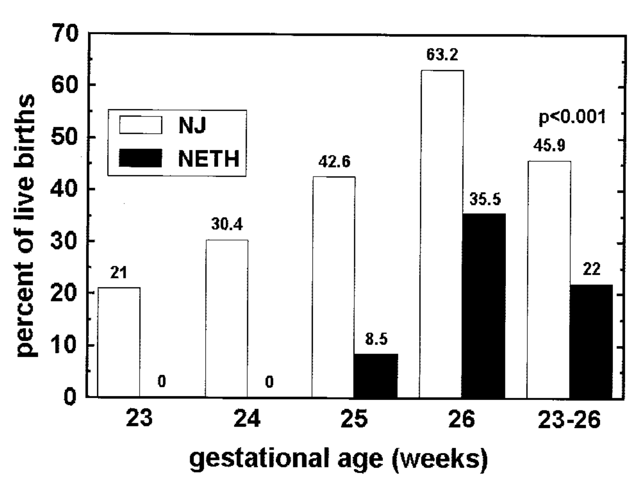

Fig 4. Survival to age 2 years.

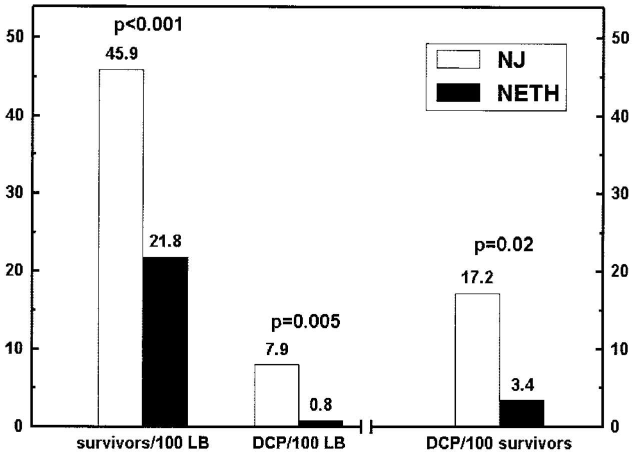

Fig 5. Survival and prevalence of DCP among live births and among survivors.

difference adjusted for preeclampsia/pregnancy-induced hypertension and race was 13.3% (95% CI: 3%–24%; $P = .015$).

The diagnosis of DCP at 2 years in NJ was based on the nurse practitioner's assessment and the Bayley psychomotor index in the 9 of the 10 survivors with DCP. In 4 of these 9, the diagnosis of CP was confirmed by a consulting neurologist; in 5 it was confirmed by medical record review. One survivor was classified as having DCP on the basis of medical record review alone. Nine of the 10 children classified as having DCP at age 2 were also seen at age 9; all 9 were classified by the examining nurse practitioner as having definite CP. Six children were clearly disabled at age 9: 4 used wheelchairs, 1 used braces, and 1 needed physical help with eating, dressing, and bathing. The remaining 3 were recorded as having difficulty keeping up with other children in sports, having motor delays, or having some limitation of normal activities. No other Dutch survivor other than the 1 child with DCP noted earlier had any limitation of normal activities as the result of CP when assessed at age 5.

Nine of the 10 cases of DCP occurred in survivors greater than 24 weeks' gestation in NJ; 5 of 31 males and 5 of 27 male survivors had DCP. The sole survivor in NETH was a boy born at 25 weeks' gestation. No child who survived without mechanical ventilation had DCP in either cohort.

Resource Expenditure

Significantly more ventilator days were expended per 100 live births (1820 vs 448 days, $P < .001$) in NJ than in NETH, but the difference in nonventilator days expended did not reach statistical significance (3175 vs 2265 days, $P = .11$). Fifty-seven additional ventilator and 37.8 additional nonventilator days were expended for each additional survivor in NJ compared with NETH; 81.1 additional ventilator and 53.8 additional nonventilator days were expended for each additional survivor without DCP in NJ compared with NETH.

DISCUSSION

The management of extreme prematurity in 2 contemporaneous cohorts in NJ and NETH was found to be very different. The more liberal use of tocolysis in NETH (usually without EFM) and the paucity of cesarean section deliveries, in contrast to the less frequent use of tocolysis, universal use of EFM, and a higher prevalence of cesarean section delivery in NJ, suggest that the obstetric management strategy in NJ focused on delivering a live infant, whereas in NETH it focused on prolonging the pregnancy. This difference in obstetric approach was paralleled by differences in neonatal management strategies. Many infants died without initiation of assisted ventilation in NETH; intensive care was documented to have been not initiated in 20% of the study population in NETH and withdrawn after initiation from another 25%. Although no direct information is available about withdrawing care in NJ, assisted ventilation was more universally initiated in NJ. These differences in strategy were associated with twice the survival rate but 10 times as many cases of DCP per 100 live births and a risk difference for DCP among survivors of 13.3 (95% CI: 3%–24%) in NJ compared with NETH, with an expenditure of >4 times as many days of assisted ventilation. At the same time, the number of additional survivors in NJ without DCP was more than twice the number of additional survivors with DCP.

Compared with that in most published studies,[4,17–24] the prevalence of DCP was not unusually high in NJ; it was lower in NETH than has generally been found. Two reasons can be posited for the lower risk of DCP with more limited use of intensive care. The first is that infants at particularly high risk of DCP were identified and allowed to die in NETH, resulting in survival of fewer infants at high risk of DCP. Although this is likely to explain some of the lower risk in NETH, a second possible contributing factor is that some aspect of neonatal intensive care practiced in NJ promoted the development of DCP. It has been suggested that the pain and stress of neonatal intensive care can worsen neurologic outcome.[25,26] It is also possible that some aspect of the ventilatory process is damaging. All survivors with DCP in both cohorts were ventilated. Greater use of assisted ventilation in NJ may have been associated with a higher prevalence of hypocapnia, which has been found to be associated with cerebral white matter damage and CP in the NBH cohort[27] and in other studies.[28–32] The hypothesis that DCP rates were lower in NETH because of lesser exposure to hypocapnia could not be explored further because Pco_2 values were not recorded in the POPS cohort.

The advantages and disadvantages of near universal initiation of neonatal intensive care summarized at the beginning of this article were borne out in this study. Survival, both with and without disability, and neonatal resource expenditure were greater. Rhoden[1] has suggested that the "least-worst" strategy is an individual one: initiate intensive care, gather prognostic information, and then reassess the decision to treat and withdraw care as indicated.

However, there are at least 2 difficulties with this strategy. First, the ability to prognosticate in individual cases is severely limited. Although the likelihood of survival improves markedly if the first week is survived,[33,34] predictive ability for developmental disabilities remains poor.[35–46] Second, some aspects of neonatal intensive care may improve survival but worsen long-term outcomes.

The management strategies used in central NJ and NETH probably are near the extreme ends of a range of approaches to the care of the extremely premature infant in the mid-1980s. However, both approaches are still considered valid. Some centers in the United States advocate initiating intensive care in most if not all infants born at 23 to 26 weeks' gestation. Although intensive care has been more commonly offered to extremely premature infants in NETH since the mid-1980s, centers in that country have recently reverted to a practice of initially offering only warmth and dextrose water infusion—not mechanical ventilation—to infants born at <25 or 26 weeks' gestation.[47] Resource expenditure with aggressive management of extremely premature infants may now be less per survivor with increasing survival[4] and the moves toward minimizing the use of mechanical ventilation and shortening length of stay. However, the effect of these factors on the prevalence of DCP among survivors is not known.

A randomized trial to provide a definitive assessment of selective initiation of intensive care probably would be unacceptable to parents and caregivers. Therefore, we have assessed this issue by the most feasible rigorous design: a prospective evaluation of contemporaneous population-based cohorts who received systematically different approaches to neonatal intensive care and whose outcomes were rigorously assessed.[48] The limitations of the study include a sample size that is not large enough to provide highly precise estimates of treatment effects, absence of information about withdrawal of intensive care in NJ, and the possibility that unmeasured demographic factors or medical variables besides selectiveness of care contributed to differences in outcome and resource expenditure.

CONCLUSION

Increased survival with near universal initiation of intensive care seems to come at the price of significantly increased resource expenditure, a greater number of disabled survivors, and a greater risk of disability in survivors. On the other hand, the more selectively intensive care is used, with a view to decreasing the prevalence of survivors with severe disabilities, the greater the number of infants who die who might have survived without severe disability had they received intensive care. If this dilemma is viewed solely as a problem in screening, setting aside for the moment ethical issues, a predictor with high negative predictive value for disability among survivors is needed to minimize the number of disabled survivors. However, positive predictive value will be low when negative predictive value is high because purported predictors of major disability are imperfect, and the majority of survivors have neither indicators of poor outcome nor poor outcome. Although this has not been documented to date,[4,19,20] there is hope that refinement of neonatal intensive care ultimately will decrease the prevalence of disabilities among survivors. Until that happens, we are confronted with a moral dilemma to which there are no easy answers and about which reasonable people can disagree.

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"On Doctoring," edited by Dr Richard Reynolds and Dr John Stone, Simon & Schuster, $35. . . . And, in W. H. Auden's lament, there is a cry for honesty in the doctor-patient relationship with which many a weary patient can identify:

"Give me a doctor, partridge-plump,
Short in the leg and broad in the rump,
An endomorph with gentle hands,
Who'll never make absurd demands
That I abandon all my vices,
Nor pull a long face in a crisis,
But with a twinkle in his eye
Will tell me that I have to die."

Langone J. *New York Times* (Books on Health Section). August 21, 2001