Chapter 3

Effectiveness of Neonatal Intensive Care

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INTRODUCTION

The remarkable decline in infant and neonatal mortality in this country since 1960 is chronicled in the OTA assessment, *Healthy Children: Investing in the Future (170).* Neonatal mortality rates (deaths during the first 28 days of life per 1000 live births) are affected by both birthweight distribution and birthweight-specific mortality rates. Assuming that better neonatal and obstetrical care imply improved outcomes for infants at a given birthweight while shifts in birthweight distribution toward heavier babies can be attributed to improved prenatal care and maternal health and nutrition, the concern in this case study is the direction of the birthweight-specific mortality rates.

Improvements in the birthweight-specific mortality rates accounted for 91 percent of the overall decline in neonatal mortality between 1960 and 1980 (27). Moreover, two-thirds of the decline in birthweight-specific neonatal mortality resulted from improved survival of low birthweight infants. Decreases in the mortality rates of infants weighing between 1500 and 2500 grams contributed more than any other weight group, including the very low birthweight group, because of both greater proportional decreases and higher absolute declines in mortality (184). In reviewing perinatal mortality rates by birthweight between 1960 and 1977 in California, Williams and Chen concluded that much of the decline could be attributed to the advent of neonatal intensive care (as well as the increased rate of cesarean section) (184).

The effectiveness of neonatal intensive care must be measured not only by whether more lives are being saved but also by whether the long-term health outcome for the babies and their families is good. The health status of survivors, specifically the rate of serious disability or handicap, has been the subject of intense interest. For the larger low birthweight infants, those with birthweights between 1500 and 2500 grams, neonatal intensive care has been accepted as a mature and effective technology (25,166). But because the risk of handicap increases with decreasing birthweight, debate continues about providing universal care for all very low birthweight infants (151,25).

This chapter focuses on changes in mortality and morbidity over the past 25 years for such very low birthweight infants. Following discussions of mortality and handicap rates, the three leading causes of mortality and morbidity in the neonatal intensive care unit (NICU) are examined in detail: respiratory distress syndrome, intraventricular hemorrhage, and retinopathy of prematurity. These clinical problems not only account for the majority of deaths among very low birthweight infants, but they can also lead to substantial long-term disabilities. The outlook for technological advances in these areas is also discussed.

MORTALITY RATES

Birthweight-specific death rates on a national basis are not available for trend analysis because not all States routinely link birth certificates (where birthweight is noted) with death certificates. However, many individual Level III centers report their experiences in the medical literature. Because the mortality rates for infants born in the Level III hospitals are lower than the mortality rates for infants who do not have immediate access to care in the intensive care units (see ch. 5), these institutional reports may be the best indicator of the impact of NICUs on mortality outcomes.

There are problems, however, in comparing mortality results from one hospital to another because of differences in the demographic charac-

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teristics of the populations served, in the standards of care, in the proportions of high-risk pregnancies, and in the selective application or withdrawal of intensive treatment measures **(83). Displaying the data by birthweight group does not completely control for these differences. For example, the distribution of gestational age within** a given birthweight group is probably the most important indicator of survival. Moreover, individual nurseries typically report on only small numbers of infants, and mortality rates may fluctuate from year to year. Bearing in mind these caveats, OTA reports and combines institutional data to permit generalization about mortality rates over time.

Table 7 summarizes reports on mortality for very low birthweight infants born in Level III hospitals (inborn) during the past 10 years. Table 8 is a similar compilation, but it lists studies that report on admissions to NICUs (inborns and transfers). The two kinds of denominator populations are reported separately for several reasons. On the one hand, inborn populations would be expected to have higher mortality rates because of the high proportion of infants who die almost immediately in the delivery room and are never admitted to the NICU. On the other hand, while the infants admitted to the NICU have survived through the first critical minutes or hours of life, the infants born in other hospitals (transfers) may be selectively sicker because of the period of time that they were denied intensive care before and during transport. A study in New York City on the effect of place of birth on mortality in fact supports both these conclusions which are further discussed in chapter 5 of this case study (119). In OTA's literature review, inborn populations had significantly lower pooled mortality rates (for 1980 to 1985) than NICU populations in the 750- to 1000-gram and the 1001- to 1500-gram birthweight groups. The differences between the two kinds of nursery populations were not statistically significant in the smallest babies born weighing under **750 grams.**

With one exception, there has been steady and statistically significant improvement in mortality rates among very low birthweight infants throughout the last 10 years. In 1985, a baby born with a birthweight between 1001 and 1500 grams has a 90 percent chance of surviving. The most substantial improvement of the 1980s over the late 1970s, in neonatal mortality rates is in the 751- to 1000-gram birthweight group where today's infants have about a 70 percent chance of surviving if they are admitted to an NICU.

The exception to the mortality decline over the past decade is among the tiniest inborn babies, those in the under *750* gram group, where some extremely promising, but mostly variable, results are reported on babies born in the 1980s.[1] For this birthweight group, Columbia University reports only 28 percent of their inborn infants died in 1986 and the University of Missouri-Kansas City School of Medicine shows only a 53 percent neonatal mortality rate in **1983 and 1984 (46,80). However, other institutions which report their experiences in the 1980s show much worse mortality rates. The 1980-85 pooled results for both denominator populations show that about two-thirds of this birthweight group dies.** Such wide variation among centers may mean that the technology of neonatal intensive care is continuing to change rapidly.

Table 9 shows the great progress that medicine has made over the past several decades in reducing birthweight-specific mortality rates among very low birthweight infants.[2] The pooled institutional results on mortality from 1961 through 1975 are taken from an earlier OTA literature review (25). Mortality for infants with birthweights of 1001 to 1500 grams has fallen from more than 50 percent in 1961 to only 10 percent today. And whereas more than 90 percent of all infants weighing under 1000 grams died in 1961, the inborn ne-

I Even for this birthweight subgroup (under 750 grams), the pooled mortality rates calculated for NICU populations decreased significantly from 1975-80 to 1980-85.

'It should be noted that improvements in the birthweight-specific mortality rates may also be attributable to factors other than solely neonatal intensive care. For example, healthier cohorts of low birthweight infants may be delivered through selective abortion, better obstetrical techniques, improved maternal care and nutrition, and so forth (18). It is not possible to sort through each factor's relative contribution, but clearly neonatal intensive care is very important.

Table 7.—Comparative Neonatal Mortality for Very Low Birthweight Infants Born in Level III Hospitals, 1975-85

Reference[b]	Year of birth	Birthweight (grams) 501-750[a] Deaths/births	Percent	751-1000[a] Deaths/births	Percent	< 1000 Deaths/births	Percent	1001-1500[a] Deaths/births	Percent
Knobloch (83)	1975-79	—	—	50/74	68 "/0		—	61/211	290/o
KOOPS (85)	1974-80	60/82	73 "/0	49/108	45 "/0	109/190	57 "/0	58/348	17"/0
Phibbs (129)[c]	1976-78	—	—	—		18/35	51 "/0	10/82	12"/0
Kitchen (82)[c]	1977-78	47/62[d]	760/o	30/65	[d]460/o	771127	61 o/o	33/250	13"/0
Nelson (1 13)	1977-78	—		·	—	220/360	61%	1221720	17"/0
Buckwald (24)[c]	1977-81	50/90	[d]560/o	—	—	—	—	—	—
Hoskins (71)	1979-80	20/39	51 "/0	14167	21 "/0	34/106	320/o	—	—
Pooled subtotal	1975-80	1771273	65%	143/314	460/o	458/818	560/o	284/1,611	180/0
Brans (22)	1978-82	68177	880/0	49/105	480/o	117/182	640/o	411236	17"/0
Avery (6)[c]	1983	31/50d	62%	71/46[d]	15"/0	38/96	40 "/0	13/109	12 "/0
Kilbride (80)	1983-84	46/87[d]	53 "/0	—		—	—	—	—
Horbar (69)[e]	1983-84	—		88/357	[d]250/o	—	—	101/1,243	80/0
Hack (61)[c]	1982-85	57/77	74%	24173	33 "/0	81/150	54 "/0	30/216	14 "/0
Driscoll (46)[c]	1986	5/18[d]	280/o	2/21[d]	10 "/0	7/39	180/0	1/75	1%
Pooled subtotal	1980-85	2071309	670/o	1701602	280/o	2431467	520/o	186/1,879	10%

[a]Some studies reported birthweight categories as 500 to 749, 750 to 999, and 1000 to 1499 g
[b]See references in the back of this case study for full citations.
[c]Deaths reported to hospital discharge.
[d]Includes birthweight categories 501 to 800 g and 801 to 1000 g
e Report on multiple neonatal intensive care centers.

SOURCE: Off Ice of Technology Assessment, 1987

Table 8.—Comparative Neonatal Mortality in Neonatal Intensive Care Units for Very Low Birthweight nfants, 1975-85

Reference[b]	Year o' birth	Birthweight (grams) 50'-750[a] Deaths/ admissions	50'-750[a] Percent	75'-1000[a] Deaths/ admissions	75'-1000[a] Percent	≤1000 Deaths/ admissions	≤1000 Percent	100' Deaths/ admissions	100' Percen'
Hack (62)	1976-78	35/44	80%	52/119	44%	87/163	53%	58/304	19%
Schechner (142)	1976-78	18/18	100%	14/28	50%	32/46	70%	14/103	14%
Britton (23)[c]	1974-77	75/90	83%	—	—	—	—	—	—
Hirata (68)	1975-80	32/60	53%						—
Philip (131)[c]	1976-79	37/48	77%	54/98	55%	91/146	62%	58/342	7%
Marlow (99)[c]	1976-80	43/46	93%	74/117	63%	117/163	72%	124/350	35%
Sell (146)[d]	1978	449/567	79%	403/813	50%	852/1,380	62%		
Bennett (13)	1977-80	76/95[e]	80%	—	—	—	—	—	—
Cohen (32,33)	1977-80	39/54	72%	33/118	28%	72/172	42%	—	—
Orgill/Yu (118,188)	1977-80	15/26	58%	32/81	40%	47/107	44%	41/280	15%
Walker (180)	1977-81	112/132[e]	85%	57/115[e]	50%	69/247	68%	—	—
Vohr (176)[c]	1978-80							39/287	14%
Stahlman (159)	1977-81	90/133[e]	68%	70/187[e]	37%	160/320	50%	—	—
Pooled subtotal	1975-80	1,021 1,313	78%	789/1,676	47%	1,627/2,744	59%	334/1,666	20%
Levi (92)	1978-81	59/71[e]	83%	—	—				
Stewart (161)	1979-84	37/59	63%	41/136	30%	78/195	40%	37/277	13%
Sell (146)[d]	1983	511/800	64%	368/1,085	34%	879/1,885	47%		—
Sandhu (141)	1983	15/20[e]	75%	14/38[e]	37%	29/58	50%	—	—
Phibbs (126)[c]	1983-84	14/22	64%	6/36	17%	20/58	34%	12/86	14%
Davidson (38)[c]	1983-84	33/44	75%	25/61	41%	58/105	55%	19/147	13%
Kraybill (86)[c d]	1984	109/149	73%	78/237	33%	187/386	48%	72/613	12%
Nichols (115)[c]	1985	21/32[e]	66%	5/9[e]	56%	26/41	63%	—	—
Pooled subtotal	1980-85	799/1. 97	67%	537/1,602	34%	1,277/2,728	47%	140/1,123	12%

[a]Some studies reported birthweight categories as 500 to 749, 750 to 999, and 1000 to 1499 g.
[b]See references in the back of this case study for full citations.
[c]Deaths reported to hospital discharge.
[d]Report on multiple neonatal intensive care centers.
[e]Includes birthweight categories 501 to 800 g and 801 to 1000 g

Office of Technology Assessment, 987.

Table 9.—inborn Neonatal Mortality Rates for Very Low Birthweight Infants, Pooled Institutional Data

	Birthweight (grams)			
	< 1000		1001-1500	
Year of birth	Deaths/births	Rate[a]	Deaths/births	Rate[a]
1961-65	1851197	939	1421274	518
1966-70	381/443	860[b]	2121567	374[b]
1971-75	209/274	763[b]	541253	213b
1976-80	4581818	560[b]	284/1,611	176
1981-85	2431467	520	186/1,879	99[b]

[a]Rate deaths/1,000 live births
[b]Significantly d! fferent from preceding 5-year rate (P < 001)

SOURCES For years 1976.85, Off Ice of Technology Assessment (see table 7) For years 1961.75, P Budetti, P McManus N Barrand et al , The Costs *and Effectiveness of Neonatal Intensive Care* (Health Technology Case Study #10), prepared for the Off Ice of Technology Assessment, U S Congress, OTA. BP-H-9 (Springfield, VA: National Technical Information Services, August 1981)

onatal mortality rate now is about 52 percent.[3] This achievement reflects improvements primarily in the 750- to 1000-gram birthweight group since mortality is still very high in the smallest and most premature infants, those under 750 grams. Neonatologists are justifiably proud of breaking the 1000 gram barrier, and they look now to infants weighing under 800 grams as their great challenge.

[3]The true neonatal mortality rate today for newborns weighing under 1000 grams who have access to neonatal intensive care is probably closer to 47 percent, the rate shown in table 8 for NICU populations. OTA used the 52 percent rate (from table 7 for inborn populations with birthweights under 1000 grams) in table 9 to be consistent across time and denominator populations. Several of the studies in table 7 showing the best survival rates for inborn populations did not report on all infants with birthweights between 500 and 1000 grams. The results of these studies could not be included in the pooled total for infants with birthweights under 1000 grams, and thus the 52 percent rate probably overestimates mortality,

HANDICAP RATES

When neonatal intensive care was introduced, concern was expressed that many sick and premature infants, who otherwise would have died, would be saved and result in a large number of handicapped children. Early, well-publicized studies of very low birthweight babies born in the 1940s and early 1950s, long before the era of neonatal intensive care, fueled this concern because they showed very high rates **(30 to 40 percent) of cerebral palsy and other forms of impairment** in survivors (45,95). Two groups, Budetti and his colleagues in their earlier OTA assessment of neonatal intensive care and a team of British researchers, independently attempted to resolve this question by reviewing published reports from hospital nurseries that described outcomes for very low birthweight infants who were born after 1945. Both review articles found that the handicap rate from the very early period dropped sharply by the mid-1960s (possibly before neonatal intensive care was widely introduced). Furthermore, from the mid-1960s through about 1977, the proportion of very low birthweight survivors with serious handicaps remained stable and relatively low (about 14 percent of survivors or from 6 to 8 percent of live births) (25,162).

These reviews were reassuring in that the introduction of neonatal intensive care apparently had not increased the proportion of survivors who are seriously handicapped. However, the two reviews covered mortality outcomes only for infants born before **1977. At that time, no published data were available on outcomes for infants with birth**weights below 800 grams, perhaps because so few such infants survived. Moreover, mortality rates have continued to drop significantly over the last 10 years for all birthweight groups under 1500

grams, and the possibility exists that infants, who previously would have succumbed because of their problems, are now rescued through new technology and contribute to the incidence of survivors with neurological damage. To determine whether handicap rates have changed during the late 1970s and the 1980s, OTA reviewed the literature for reports on morbidity outcomes for infants born between 1975 and 1985. The results are shown in tables 10 through 12 by birthweight group.

Like birthweight-specific mortality data, birthweight-specific morbidity data are not collected on a routine basis in the United States. Thus reports from individual nurseries are the only available data source that reflects the long-term morbidity of very low birthweight infants. All of the shortcomings discussed previously for the institutional data on mortality hold as well in using and pooling morbidity data from individual nurseries. Differences in the character and experiences of the study populations yield different results. Moreover, comparisons of morbidity are further complicated by the different ways in which outcome is measured and reported. There are differences in the definitions of abnormalities, in the details with which diagnostic categories are specified, in the ages at which followup examinations are done, and in the measures used in the neurodevelopmental evaluations (78,83).

The interrelationship of mortality and morbidity is especially difficult to interpret. It is likely that neonatologists' attitudes and decisions concerning termination of life support for very low birthweight infants who manifest severe neurological dysfunction are a major factor in determining the rate of serious morbidity among survivors. Thus, a comparatively high neonatal mortality rate might be expected to be associated with a relatively low rate of handicap. Although several reports on the under 800-gram population fit this hypothesis (13,60,61), just as many studies reported relatively high survival and low handicap rates (68, 79,80, 161). Overall OTA found no consistent relationship between mortality and the rate of serious morbidity in its literature review,

Determinations of long-term morbidity and disability cannot be made at hospital discharge. The extent to which researchers were able to follow NICU survivors through the first few years of life and classify their disabilities varied from study to study. In general, followup rates were highest in the studies reporting on the smallest birthweight infants. This is because the tiniest babies are less numerous and tend to have problems that encourage their families to seek ongoing medical care. Conversely, a larger percentage of the NICU survivors with birthweights between 1000 and 1500 grams were lost to followup, but many of these infants are normal. In all three birthweight groups examined by OTA, a substantial portion of the infants lost to followup died during the postneonatal period. Although many of the deaths were directly related to complications of prematurity and intensive care treatment, sudden infant death syndrome (SIDS) was also a major cause of death after hospital discharge. The high postneonatal mortality rate experienced by very low birthweight infants, perhaps 10 to 15 times that found among normal birthweight infants, is not well understood by medical researchers (170,188).

OTA adopted the definitions of handicap used by the reviewers in the earlier OTA assessment in order to categorize disparate reports. "Serious handicaps" are defined as: severe mental retardation (IQ or developmental quotient below 70); cerebral palsy of significant degree (spastic diplegia, paraplegia, tetraplegia, hemiplegia); major seizure disorders; blindness; and severe hearing defects (25). "Moderate handicaps" are narrowly defined to include all infants with a developmental quotient or IQ between 70 and 80. No attempt was made in this review to capture the "mild" impairments that many very low birthweight infants develop later in early childhood or even at school age because most published reports follow NICU survivors only to 2 or 3 years of age (68). It should be noted that there is a higher incidence of such relatively mild handicaps, which include behavioral, learning, and language disorders, in very low birthweight infants than in normal birthweight children (116).

The incidence of serious handicap increases significantly with decreasing birthweight (tables 10 to 12). For infants born between 1975 and 1985, OTA found that 26 percent of surviving infants with birthweights below 800 grams, 17 percent

Table 10.—Handicap Rates in Infants With Birthweights Under 800 Grams, 1975-85

Reference[c]	Year of birth	Infants surviving to hospital discharge		Survivors followed after hospital discharge					
				Total		Children with serious handicaps[a]		Children with serious or moderate handicaps[b]	
		Number	Percent	Number	Percent[d]	Number	Percent[e]	Number	Percent[e]
Saigal (139)[f]	1973-78	5[g]	(10%)	4	(80%)	1	(25%)	2	(50%)
Britton (23)	1974-77	39	(25%)	37	(95%)	8	(22%)	18	(49%)
Hirata (68)[f]	1975-77	24	(40%)	18	(75%)	3	(17%)	6	(33%)
Marlow (99)[f]	1976-80	3	(7%)	3	(100%)	1	(33%)	NA	—
Bennett (13)	1977-80	19	(20%)	16	(84%)	2	(13%)	4	(25%)
Cohen (32)[f]	1977-80	12	(28%)	9	(75%)	3	(33%)	3	(33%)
Saigal (140)	1977-80	41[g]	(29%)	38	(93%)	13	(34%)	20	(53%)
Orgill (118)[f]	1977-80	11	(42%)	11	(100%)	3	(27%)	3	(27%)
Walker (180)	1977-81	20	(15%)	20	(100%)	6	(30%)	8	(40%)
Buckwald (24)	1977-81	65	(45%)	54	(83%)	19	(35%)	31	(57%)
Kraybill (87)	1980	4	(24%)	4	(100%)	1	(25%)	1	(25%)
Levi (92)	1978-81	12	(17%)	10	(83%)	2	(20%)	2	(20%)
Stewart (161)	1979-83	16[h]	(27%)	12	(75%)	2	(17%)	NA	—
Hack (60,61)[f]	1982-85	20	(26%)	18	(90%)	2	(11%)	4	(22%)
Pollara (132)[f]	1983-84	3	(8%)	2	(67%)	1	(50%)	1	(50%)
Kilbride (79,80)	1983-84	41	(47%)	34	(83%)	8	(24%)	11	(32%)
Pooled total	1975-85			290		75	(26%)	114	(41%)[i]

[a]Serious handicaps are defined as the following: severe mental retardation (IQ or developmental quotient below 70); cerebral palsy of significant degree; major seizure disorders; or blindness.
[b]Serious or moderate handicaps includes all those handicaps defined above as serious plus a developmental quotient or IQ between 70 and 80.
[c]See references in the back of this case study for full citations.
[d]Of those infants surviving to hospital discharge.
[e]Of survivors followed after hospital discharge.
[f]Includes infants with birthweights between 500 and 750 grams.
[g]Survival calculated on regional population of births.
[h]Survived to end of first year.
[i]Denominator population is 275 infants.

SOURCE: Office of Technology Assessment, 1987.

Table 11.—Handicap Rates in Infants With Birthweights Between 750 and 1000 Grams, 1975-85

Reference[c]	Year of birth	Infants surviving to hospital discharge		Survivors followed after hospital discharge					
				Total		Children with serious handicaps		Children with serious or moderate handicaps	
		Number	Percent	Number	Percent[d]	Number	Percent[e]	Number	Percent[e]
Saigal (139)	1973-78	32[f]	(49%)	31	(97°/0)	4	(13%)	10	(32%)
Knobloch (83)	1975-78	—		9		5	(55%)	6	(67%)
Marlow (99)	1976-80	43	(37%)	40	(93%)	10	(250/o)	NA	—
Orgill (118)	1977-80	48	(59%)	48	(100%)	7	(15°/0)	10	(21 %)
Cohen (32)	1977-80	84	(720/o)	72	(86°/0)	4	(6°/0)	18	(25%)
Saigal (140)[g]	1977-80	76[f]	(67%)	72	(95°/0)	13	(18°/0)	35	(49%)
Walker (180)[g]	1977-81	58	(50%r)	48	(83°/0)	5	(10%)	10	(21%)
Kraybill (87)[g]	1980	26	(670/o)	25	(96°/0)	3	(12%)	7	(28%)
Stewart (161)	1979-83	73[h]	(54%)	54	(74%)	7	(13%)	NA	—
Pollara (132)	1983-84	44	(690/o)	35	(80°/0)	17	(49%)	NA	—
Pooled total	1975-84			434		75	(17%)	96	(31%)[i]

[a]Serious handicaps are defined as the following: severe mental retardation (IQ Or developmental quotient below 70); cerebral palsy of significant degree; major Seizure disorders, Or blindness
[b]Serious or moderate handicaps Includes all those handicaps defined above as serious PIUS a developmental quotient Or IQ between 70 and 80.
[c]See references in the back of this case study fOr full citations
[d]Of those infants surviving to hospital discharge
[e]Of survivors followed after hospital discharge.
[f]Survival calculated on regional population of births.
[g]Includes infants with birthweights between 500 and 800 grams
[h]Survived to end of first year.
[i]Denominator population is 305 infants.

SOURCE Office of Technology Assessment, 1987

Table 12.—Handicap Rates in Infants With Birthweights Between 1000 and 1500 Grams, 1975-85

				Survivors followed after hospital discharge					
		Infants surviving to hospital discharge		Total		Children with serious handicaps		Children with serious or moderate handicaps	
Reference[c]	Year of birth	Number	Percent	Number	Percent[d]	Number	Percent[e]	Number	Percent[e]
Hack (62)	1975-76	153	(76%)	128	(84%)	20	(16°/0)	NA	—
Saigal (139)	1973-78	147[f]	(83%)	131	(89%)	6	(5%)	26	(20%)
Knobloch (83)	1975-78	—		79		15	(19%)	28	(35%)
Sherman (152)	1976-77	34	(81%)	26	(76%)	NA		3	(12%)
Marlow (99)	1976-80	226	(65%)	210	(93%)	27	(13%)	NA	
Powell (133)	1979-81	285[f]	(73%)	276	(97%)	NA		31	(11%)
Stewart (161)	1979-83	227[g]	(82%)	168	(74%)	9	(5%)	NA	
Crombie (36)	1979-83	108	(82%)	77	(71%)	3	(4%)	5	(6%)
Pollara (132)	1983-84	165	(85%)	120	(73%)	20	(17°/0)	NA	—
Pooled total	1975-85			1,215		100	(11%)[h]	93	(16%)[i]

[a]Serious handicaps are defined as the foll owin Q: severe mental retardation (IQ or developmental quotient below 70); cerebral palsy of significant degree, major seizure disorders; Or bli ndness
[b]Serious or moderate handicaps includes all those handicaps defined above as serious plus a development} quotient or IQ between 70 and 80
[c]See references in the back of this case study fOr full citations.
[d]Of those Infants surviving to hospital discharge
[e]Of survivors followed after hospital discharge
[f]Survival calculated on regional population of births
[g]Survived to end of first year.
[h]Denominator population is 913 infants.
[i]Denominator population is 589 infants.

SOURCE Off Ice of Technology Assessment, 1987

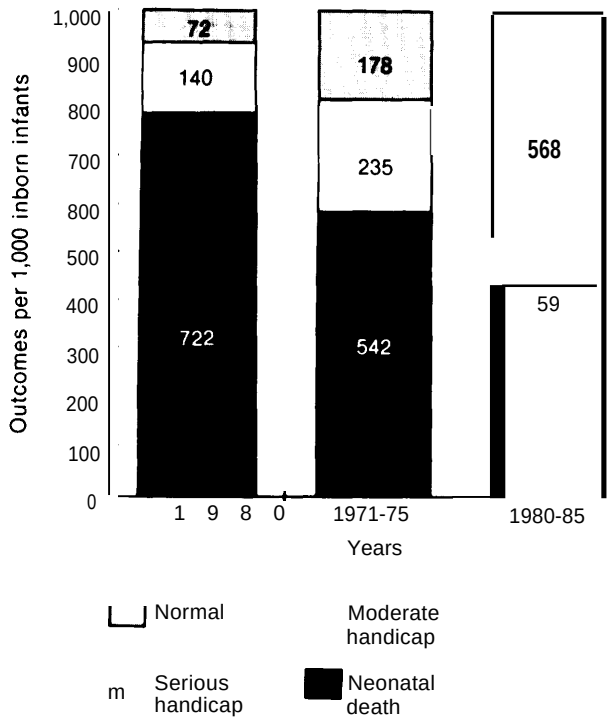
of survivors with birthweights between 750 and 1000 grams, and 11 percent of survivors with birthweights between 1000 and 1500 grams have major disabilities at 1 or 2 years of age. Of the surviving infants with birthweights under 800 grams, 41 percent have either a moderate or severe handicap, while only 16 percent of the survivors with birthweights between 1000 and 1500 grams are so handicapped.

These results corroborate the conclusions of Budetti and his coworkers (25). Within each birthweight group, the proportion of survivors with serious handicaps has not changed significantly since the mid-1960s. The earlier review did not report on infants with birthweights under 800 grams, so comparisons over time cannot be made for this birthweight group. The group of infants that was labeled in the earlier review as weighing less than 1000 grams almost exclusively included infants with birthweights between 750 and 1000 grams; the pooled rate of serious handicap for this birthweight category has not changed significantly from 1965-75 to 1975-85 (16 to 17 percent). Today, however, many more infants with birthweights below 800 grams are living and contributing both relatively more normal and handicapped children to the pool of survivors with birthweights under 1000 grams.

The conclusion that, within birthweight group, the rate of serious handicap among survivors has not changed significantly over time masks the contribution that neonatal intensive care probably has made to improved morbidity, as well as improved mortality, outcomes. Since many very sick babies who previously would have died are now surviving, *increasing* handicap levels **among survivors should be expected.** The finding of constant levels of handicap therefore points to the increasing effectiveness of neonatal intensive care for the long-term developmental outcomes for these children.

Figures 2 and 3 demonstrate graphically the effects of declining mortality on the relative proportions of normal and abnormal survivors.[4] The absolute numbers of both normal and seriously handicapped children increase. Infants with birthweights between 1000 and 1500 grams make up about 54 percent of all very low-weight births in the United States each year. Because of their relative numerical strength, the comparatively lower handicap rates of this "larger" infant group moderate the overall rates of disability among all very low birthweight infants. For example, with birth rates at the 1984 level, if today's neonatal intensive care was provided for all very low birthweight infants, about 2,200 seriously handicapped children would survive who would have died in 1975. This figure must be balanced against the 15,200 net increase in normal infants who would also survive under current conditions. The overwhelming majority of survivors in both the under 1500-gram and the under 1000-gram birthweight groups are normal.

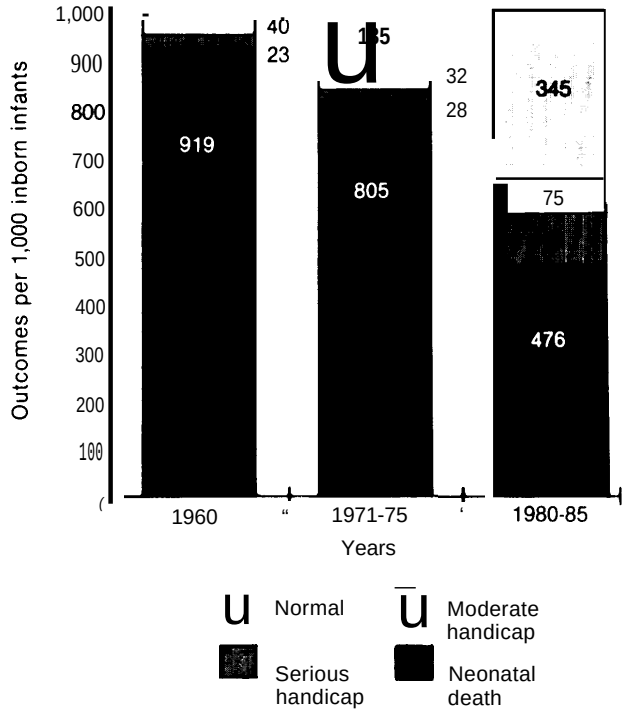
Figure 2.—Outcomes for Very Low Birthweight Infants (< 1500 gram) Born in Level III Hospitals, 1980-85



SOURCES: For years 1980-85, Office of Technology Assessment (see tables 7. 10, 11, and 12). For years 1980 and 1971-75, P. Budetti, P. McManus, N. Barrand, et al., *The Costs* and *Effectiveness of Neonatal Intensive* Care (Health Technology Case Study #l O), prepared for the Office of Technology Assessment, U.S. Congress, PB 82-101411 (Springfield, VA: National Technical Information Service, August 1981).

[4]Figures 2 and 3 reflect mortality and morbidity outcomes for very low birthweight infants who are born in Level 111 hospitals and have access to neonatal intensive care. Neonatal mortality rates for the general population of very low birthweight infants are significantly higher, and morbidity outcomes are unknown. Postneonatal mortality is not reflected in the figures, although such deaths probably have a substantial impact on overall outcome rates.

Figure 3.—Outcomes for Extremely Low Birthweight Infants (< 1000 grams) Born in Level III Hospitals, 1960-85



SOURCES For years 1980.85, Off Ice of Technology Assessment (see tables 7, 10, 11, and 12) For years 1960 and 1971-75, P Budetti, P McManus N Barrand, et al , The Costs *and Effectiveness of Neonatal Intensive Care* (Health Technology Case Study #10, prepared for the Off Ice of Technology Assessment, U S Congress, PB 82-101411 (Springfield, VA National Technical Information Service, August 1981)

NEONATAL CONDITIONS THAT CAUSE MAJOR MORTALITY AND MORBIDITY

Deaths among very low birthweight infants in intensive care are caused primarily by two conditions, respiratory distress syndrome and intraventricular hemorrhage. These conditions, along with retinopathy of prematurity, are also responsible for most of the long-term disabilities that plague NICU survivors. The sophisticated technology used in neonatal intensive care saves lives but also can exacerbate or even, in some cases, precipitate these problems. The application or withholding of such technologies presents an ongoing ethical dilemma for neonatologists.

Respiratory Distress Syndrome

Respiratory distress syndrome (RDS) is the most common problem in the neonatal nursery and the primary cause of mortality. It accounted for 18 percent of all neonatal deaths in 1978 (122). For babies weighing under 1000 grams, over 60 percent of the deaths have been attributed to RDS or to intraventricular hemorrhage, and for babies in the 1000- to 1500-gram category, 25 percent of the deaths are blamed on these causes (11).

Photo credit: Strong Memorial Hospital, Rochester, NY

Premature infants with severe respiratory distress syndrome usually require assisted ventilation.

Very premature infants experience respiratory distress because they lack an essential substance in the lung (or pulmonary surfactant) that reduces the surface tension along the alveoli and prevents the collapse of the pulmonary air spaces. The immense strain of having to force the alveoli open with each breath makes it increasingly difficult for these tiny babies to breathe independently. The pulmonary surfactant does not begin to coat the fetus's alveoli until between the 24th and 28th weeks of gestation, and it is not produced in major amounts until the 33rd week.

RDS occurs in 14 to 60 percent of premature deliveries at gestational ages between 28 and 35 weeks (174). Individual clinical centers report an even higher incidence of RDS among the extremely low birthweight babies. Kitchen and his associates reported an overall RDS incidence of 55 percent among the under 150&gram population **(82).** In the under 1000-gram group, Vohr and Hack found that 82 percent and Saigal and colleagues found that 74 percent of neonatal survivors had RDS (140,176).

Infants with RDS stay in the hospital on average twice as long as those without RDS (174). In 1984 at the University of California at San Francisco perinatal center, babies with RDS stayed in the NICU almost four times longer than babies without RDS and had hospital costs more than three times higher (126).

RDS may take mild, moderate, or severe form. Its clinical course is marked by increasing oxygen need and often by the need for assisted mechanical ventilation (breathing machines) to maintain adequate oxygenation and to remove carbon dioxide. The primary problem for RDS babies is the collapse of the alveoli which makes the work of breathing increase to physiologically intolerable levels. Two respiratory therapy techniques, developed over the past 15 years, prevent alveolar collapse by keeping up positive pressure on the lungs between breaths. Continuous positive airway pressure (CPAP) is used by itself to facilitate breathing, and positive end expiatory pressure (PEEP) is used in conjunction with positive-pressure ventilation. These innovations in respiratory therapies, as well as improvements in ventilator techniques such as the now widespread use of continuous flow pressure regulated ventilators, have contributed to diminished severity of RDS (167). Deaths associated with RDS have been decreasing since 1974, though it remains the leading cause of neonatal death (122).

Bronchopulmonary Dysplasia

Mechanical ventilation is essential for the survival of babies with severe RDS, but it disrupts the babies' normal cardiopulmonary physiology. Its prolonged use leads to a chronic lung disease called bronchopulmonary dysplasia (BPD). (Other conditions besides RDS can lead to ventilation of newborns and thus to BPD; these include pneumonia, meconium aspiration, patent ductus arteriosus, and apnea of prematurity (52).) BPD was first recognized and described in the 1960s (168). By definition, all infants who require mechani-

cal ventilation during the first week of life, who remain dependent on supplemental oxygen for more than 28 days, and who have a characteristic chest radiograph have BPD (52).

BPD has become one of the most common sequelae of neonatal intensive care. A recent review article concluded that one-third of infants given mechanical ventilation and weighing less than 1500 grams at birth develop chronic lung disease (167). Two multicenter studies of 700- to 1500-gram babies in **1983 and 1984 also reported that overall about one-third of the survivors had chronic lung disease (8,10,69).** These studies found that female and black babies had significantly lower rates of chronic lung disease than their male and white counterparts in similar birthweight groups (10,69). Birthweight was the most significant predictor of lung damage. While only 19 percent of survivors with birthweights between 1000 and 1500 grams had chronic lung disease, 51 percent of survivors with birthweights between 700 to 1000 grams had BPD (69).

Reports from individual clinical centers conflict on the incidence of BPD among extremely small infants. Among the tiniest babies (under 800 grams), Buckwald and associates found that 75 percent of the survivors were still on a ventilator at 1 month, and Hack and Fanaroff reported that 70 percent of the survivors in their hospital developed BPD (24,61). On the other hand, Bennett and colleagues, also reporting on babies with birthweights under 800 grams, found only a quarter of the survivors developed BPD (13). Similarly, three reports on infants weighing less than 1000 grams found 62, 30, and 13 percent, respectively, of survivors developed BPD (140,48,71).

Significant mortality and long-term morbidity are associated with BPD during the postneonatal period **(86). Like RDS, bronchopulmonary dysplasia can take mild, moderate, or severe forms. About 1 out of 40 infants discharged from the hospital with BPD is so severely affected that respiratory support continues to be required at home (41,147). Rehospitalization and chronic respiratory problems are associated with BPD patients. Even after controlling for other risk factors like intraventricular hemorrhage, prolonged mechanical ventilation has been found to be associated** with poor developmental progress during the first 18 months of life in very low birthweight infants (21). When low birthweight infants with BPD were compared to a control group without the disease, the BPD infants had more respiratory diseases at 4 and 12 months and more severe neurodevelopmental sequelae at 2 years (177). Another study that followed BPD patients prospectively for 2 years post-term found that 85 percent of the children had lower respiratory tract infections and 50 percent of the infants required rehospitalization during their first year (98). Finally, a recent study of infants with BPD who were born between 1981 and 1983 confirmed the increased incidence of hospitalization and respiratory problems during the first year of life, but found that, for survivors, differences with the control group in neurodevelopment evident at 1 year had disappeared by 2 years of age (136).

Medical Practices

The detrimental effects of positive pressure ventilation have been known since 1965 (28). There is now some evidence that the way in which ventilatory support is medically managed may be associated with outcome. When Avery and her colleagues surveyed eight tertiary clinical care centers in **1983 and 1984 for their experience with BPD in infants weighing 700 to 1500 grams, they found that some institutions did significantly better than others (10).** Even after adjustments were made for weight distribution, sex, and race (but not for gestational age), differences among centers persisted. Among those centers studied, the intensive care unit at Columbia University had the best outcomes. At Columbia, the policies for respiratory management are dictated by a single physician, and the policies are followed at all times and for all babies. Instead of resorting to mechanical ventilation immediately, nasal CPAP is used to treat RDS early in the course of the disease and during the weaning from assisted ventilation. Attempts are made to minimize physical trauma; endotracheal tubes are used infrequently and for only short periods of time and muscle relaxants are never employed.

Medical practices and the use of technology vary widely among perinatal centers, and there are no clearly accepted norms for practice. Fur-

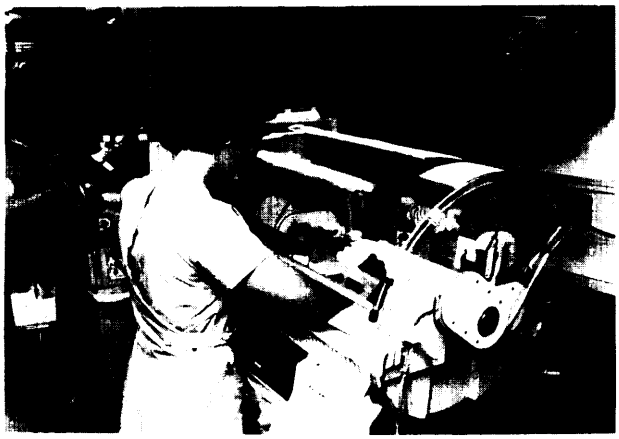


Photo credit: Strong Memorial Hospital, Rochester, NY

Coordinated management in the NICU and use of non intrusive therapies have been suggested as major factors leading to improved outcomes for very low birthweight infants.

ther systematic research is needed so that reliable comparisons among centers can be made and epidemiological methods used to evaluate ventilatory techniques (167).

Technological Advances

Improvements in existing ventilator techniques may hold promise for reducing the incidence of BPD in the future. In recent years, for example, there has been considerable research on several ventilator techniques, known collectively as high-frequency ventilation (HFV), that use rapid ventilator rates that may interfere less with normal cardiopulmonary physiology. Thus far, however, HFV has not been proven superior to conventional ventilation for treating neonates in respiratory failure **(20).**

Another new technology is extracorporeal membrane oxygenation (ECMO) which entirely bypasses the lungs using a process that closely duplicates the gas exchange function performed in utero by the placenta. ECMO can be used for as long as 2 weeks, allowing time for lung recovery by minimizing the harmful influences associated with high-pressure mechanical ventilation. ECMO has been used on more than 300 infants in 18 centers since 1975, but with very poor outcomes for premature, small infants. The incidence of intracranial hemorrhage is exceedingly high in these infants, and the bleeding may be aggravated by the heparin administered during ECMO. Unless further research can make ECMO available for infants who weigh less than 2000 grams, only small numbers of patients are likely to be treated by this technology. ECMO is currently indicated and may be lifesaving for term infants with meconium aspiration syndrome, persistent pulmonary hypertension, or diaphragmatic hernia (189).

The better solution for the problems posed by mechanical ventilation is to avoid the need for its use altogether. Two technologies are under development and testing that could substantially prevent RDS in the future. The first is the prenatal administration of glucocorticoids (steroids) to mothers in preterm labor in order to accelerate fetal lung maturation. The other technology, still experimental, is the introduction of exogenous pulmonary surfactant into the lungs of the newborn.

Steroid treatment of women in preterm labor has been used and studied for 16 years (7). Although all the studies support the efficacy of the steroids in reducing the incidence of RDS in the babies subsequently born, concerns remain about indications for use in specific situations, the influence of the steroids on infection during labor, and the effect of the steroids on the long-term development of the babies (43). Because of these concerns (particularly for patients with premature rupture of the membranes), some obstetricians use the steroids either selectively or not at all **(29).**

A multicenter, 7-year collaborative study on antenatal steroid therapy attempted to resolve these concerns. Reporting its results in 1985, the study confirmed the efficacy of steroids in reducing the incidence of RDS and in decreasing the severity of the disease in those affected. Furthermore, it found no evidence that the risk of infection is increased in the neonate or in the mother. And there is no effect of the steroid on either neurological maturation or function or developmental outcome during the first 3 years of life. However, the researchers also reported no effect on mortality and suggested that the effectiveness of steroid therapy is significant only for female offspring and only when the membranes are intact (174).

The collaborative study excluded infants under 28 weeks gestational age. A recent, retrospective study in Australia, designed to include a large number of very low birthweight infants at high risk of death, contradicted the findings of the collaborative study. It found survival is substantially improved by antenatal steroid therapy and that survival improves in both girls and boys (44).

Although the efficacy of steroid treatment is not resolved, the therapy clearly has several limitations. It does not work for all babies; at best, it lowers incidence and severity of RDS. And in addition, because steroid therapy must be initiated at least **24** hours before delivery in order to be effective, for obstetrical reasons many women in preterm labor cannot be candidates for its use.

Treating surfactant deficiency by administering exogenous natural or synthetic surfactant to the lungs of very premature babies at or soon after birth has the potential to greatly reduce the incidence of severe RDS. The basic biochemistry and physical chemistry of lung surfactant has been known for a long time, but research is ongoing for the best surfactant mixture, the optimum dose, and the timing and frequency of administration. At least seven recent randomized, controlled clinical trials testing natural surfactants (recovered from lung lavage of animals or humans) document that surfactant-treated infants have less severe RDS than control infants (51,74,84,102). The studies show a lower incidence of clinical RDS, lower ventilator requirements, and less oxygen supplementation in treated than in control infants. The treatment with human surfactant significantly decreased the risk of death and bronchopulmonary dysplasia (102). Several of the studies using bovine (cow) lung extract also showed decreases in the risk of death (158). While one recent multicenter trial in Great Britain using synthetic surfactant found reductions in mortality and the need for respiratory support **(104), other studies to date with synthetic surfactants have shown essentially no benefit for respiratory function (63,183).**

In none of the studies do all infants respond to the surfactant. Therefore, perfecting surfactant replacement will not be a panacea for RDS. Researchers hypothesize that some infants have respiratory distress from other causes, such as infection, or that, in extremely premature infants, dysfunction might by caused by other structural immaturities (9). Large-scale, multicenter trials are being undertaken in Europe and the United States to continue to test surfactant experimentally. It is probable that the necessary research and FDA approval process will take from 1 to 5 years before surfactant therapy will be generally available for preterm babies (8,149).

Intraventricular Hemorrhage

Along with RDS, intracranial hemorrhages, or brain bleeds, are responsible for the most deaths in the neonatal nursery (11). The most dangerous are intraventricular hemorrhages in which blood seeps into the cerebral ventricles, small cavities within the brain that secrete and convey cerebrospinal fluid, Almost all serious hemorrhages occur within the first or second day after birth (178). Once extensive brain damage has occurred there is little medicine can offer to improve the prognosis (178). An infrequent additional complication for babies with hemorrhage is the development of hydrocephalus, the dangerous distension of the head caused by the excessive buildup of cerebral spinal fluid. Fortunately many cases of posthemorrhagic hydrocephalus resolve spontaneously or respond to medical therapy (153).

Premature infants' blood vessels are particularly fragile, and a prevalent medical opinion is that the capillaries rupture and hemorrhage because of fluctuations in cerebral blood flow. Along with other causes including asphyxia, seizures, and pneumothorax, the use of intermittent positive pressure ventilation has been associated with hemorrhage **(42,178). It is believed by some that the infant's own respiratory effort, out of synchrony with the ventilator, causes changes in the cerebral blood pressure (123). Recent research has focused on ways, like muscle paralysis during ventilation, to prevent** such fluctuating patterns of cerebral blood flow velocity (123).

Previously recognized conclusivel, only on autopsy, the introduction of computed tomography scanning and later of ultrasound brain scanning revealed that 31 to 45 percent of infants weighing under 1500 grams at birth have subependymal or intraventricular hemorrhages (42,123). Most hemorrhages are graded mild and appear to cause

no lasting clinical problems. Estimates vary on the proportion of cerebral hemorrhages that are severe as well as on the subsequent mortality and morbidity. Mortality is clearly higher in groups of infants with hemorrhage, as compared with other infants matched for birthweight or gestational **age (101), A partial review of institutional studies completed in the 1970s reported that mortality from severe hemorrhage ranged between 50 and 65 percent and that hydrocephalus developed in 45 to 100 percent of the survivors (153). More recent studies** have shown much lower fatality rates of 13 percent (42) and 6 percent (153) from intraventricular hemorrhage. In one of these studies only one infant (6 percent of the survivors) developed progressive hydrocephalus (153), while in the other study no infant required shunting for hydrocephalus (42).

The incidence and severity of hemorrhage are correlated with gestational age and birthweight. Infants born at less than 29 weeks gestation are especially at risk (42,153). Before 32 weeks gestation, a disproportionate amount of the total cerebral blood flow enters the periventricular circulation, and thus any disturbance of the blood flow tends to cause hemorrhage in this region of the brain (178). While the association of hemorrhage with gestational age is well established and founded on physiological evidence, birthweight alone is not as good a predictor of the likelihood of hemorrhage. Only one study reported results by birthweight category. At the Johns Hopkins Hospital in 1980, 90 percent of the babies weighing between **600** and 1000 grams had cerebral hemorrhages (36 percent of the babies had severe hemorrhages), but only 26 percent of the infants weighing between 1000 and 1600 grams had hemorrhages **(6** percent severe). This study found no evidence that the 600- to 800-gram babies had more severe hemorrhages than the other infants in the under 1000-gram" category, although the tiniest babies did have the highest overall incidence of hemorrhage (49).

Neurodevelopmental Outcome

Infants with severe intraventricular hemorrhages have a high rate of later neurodevelopmental handicaps. The risk of developing neurodevelopmental defects is correlated to the initial degree of hemorrhage (30,88,121). In a study of infants weighing under 1500 grams and born between 1976 and 1981, Papile and her colleagues at the University of New Mexico concluded that infants with mild grades of cerebral hemorrhage had no poorer outcomes than other babies of similar birthweight groups without hemorrhage. But they also found a major handicap in 58 percent of the infants with severe intraventricular hemorrhage, and multihandicaps in 45 percent of this group (121). An Australian study of extremely preterm babies born between 23 and 28 weeks gestation in 1981 reported that 8 of 12 infants with severe hemorrhage (67 percent) developed major disabilities (30). The study at Johns Hopkins Hospital of low weight babies born in 1980 found less disastrous results. At 12- to 22-month followup examinations, of 11 babies who had severe hemorrhages, 6 were normal, 3 had moderately retarded development, and only 2 babies or 18 percent had serious intellectual and motor impairment (153).

Photo credit: March of Dimes Birth Defects Foundation

With appropriate therapy and support, the prognosis for even seriously handicapped very low birthweight infants improves over time.

Retinopathy of Prematurity

Another affliction affecting premature infants is retinopathy of prematurity (ROP). The disease occurs in progressive stages beginning with retinal vasoconstriction, proliferation of blood vessels, scarring (cicatricial disease) of the retina, retinal detachment, and ultimately blindness (137). The disease is not invariably progressive and blindness is by no means an inevitable outcome. Many cases spontaneously regress to normal. Perhaps **25** percent of those with cicatricial disease go on to blindness (124).

The epidemic of ROP between 1942 and 1953 which resulted in about 10,000 blind children is perhaps the most widely known example of iatrogenic disease (156).[5] Because of technological advances, it was routine during that decade to administer high concentrations of oxygen to essentially every premature infant, and it was not until 1954 that a large, multicenter cooperative study indicted oxygen as the culprit in the exponential growth of ROP. The practice of routine oxygen administration was quickly abandoned, and the oxygen administered to infants with respiratory distress was given in much lower concentrations. But while there was a sharp decline in the prevalence of ROP during the 1950s and 1960s, researchers started reporting results by the early 1960s that created increasing uneasiness with the blanket policy of oxygen restriction for all premature infants. When oxygen usage was curtailed, studies showed that neonatal mortality and the incidence of spastic diplegia (a form of cerebral palsy) increased among premature infants. It was later estimated that for every case of blindness prevented, approximately 16 babies died due to inadequate oxygenation (37).

Today's medical opinion is that the cause of ROP is unknown but likely multifactorial, with oxygen being but one critical factor. Other risk factors suspected of playing a role in the etiology of ROP include too little oxygen in utero, infection, intraventricular hemorrhage, apnea, blood transfusions, hypercarbia, hypocarbia, patent ductus arteriosus, prostaglandin synthetase inhibiters, vitamin E deficiency, assisted ventilation, lactic acidosis, and prenatal complications (97). But overwhelmingly the primary risk factor is extreme prematurity, with almost all cases confined to this vulnerable group (137). The blood vessels in the immature retina are still developing, and it is believed that any disturbance in retinal circulation, whether too much oxygen or too little, can lead to the vessels' disordered and twisted growth. The very low birthweight, premature infant suffers from a number of the risk conditions that can disturb retinal circulation, and some cases of ROP appear to be unavoidable despite careful attention to oxygen therapy and monitoring.

Advances in neonatal care methods and the survival of more small and critically ill infants have contributed to a resurgence of ROP, which some call a second epidemic (137). Infants weighing under 1500 grams at birth are at greatest risk. Both the incidence and the severity of retinal disease increases with progressively lower birthweight and gestational age.

A 1981 review of the literature estimated that among infants weighing between 1000 to 1500 grams at birth, 2,2 percent have scarring ROP and 0.3 to 1.1 percent are eventually blinded. For infants under 1000 grams, approximately 22 to 42 percent have cicatricial ROP and 5 to 11 percent are blinded (124). By contrast, a Canadian population-based study conducted from 1977 to 1980 found that only 13 percent of infants under 1000 grams developed cicatricial disease, but overall 7 percent of the survivors were blinded (140). Two more recent studies of infants in NICUs weighing under **800** grams have reported that 25 percent (61) and 10 percent (80) developed cicatricial ROP. Finally, a controlled study investigating ROP from 1977 to 1980 in an Australian NICU found a lower incidence of serious scarring in the extremely low birthweight group than previously reported. Among the infants weighing under 1000 grams, only 3 percent developed scarring ROP; unfortunately all of them were blinded. This study also found in the 1000- to 1500-gram population that 2 percent developed cicatricial disease and 1 percent was blinded (187). These incidence figures agree with Phelps' estimates.

Although no technological fix is on the horizon, there has been renewed interest since the

[5] At the time of the epidemic, the disease was called retrolental fibroplasia. This term, still in use today, refers to the proliferation of scar tissue during the latter stages of the disease.

1970s in vitamin E as a preventive measure against ROP. Vitamin E was first used to prevent ROP in 1949. Although that initial study did find a significant effect, subsequent trials failed to confirm its efficacy, and when the role of oxygen was identified by the collaborative trial in 1954, both ROP and **its possible relation to vitamin E were dropped from the research agenda (125). Lucey and Dangman reviewed five recent clinical trials that used vitamin E prophylactically to treat either very low birthweight patients or patients with RDS.** The results of these studies, though difficult to compare, are conflicting. Some showed a reduction in both incidence and severity of ROP, others showed a lessened severity with no effect on incidence, and still others found no significant effect at all on the occurrence of ROP (97). While these results offer the promise of at least reducing the worst ROP, several researchers have urged caution and extensive further research. There are suspicions that vitamin E treatment may expose premature infants to increased risks of necrotizing enterocolitis and intraventricular hemorrhage (97,125). The potential negative side effects of vitamin E may outweigh the possible benefits.