

## *Annotations*

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### CEREBRAL PALSY AND NEWBORN CARE. III: ESTIMATED PREVALENCE RATES OF CEREBRAL PALSY UNDER DIFFERING RATES OF MORTALITY AND IMPAIRMENT OF LOW-BIRTHWEIGHT INFANTS\*

A FALL in the mortality rate for low-birthweight infants as a result of medical intervention could, in theory, either increase or decrease the prevalence of neurological impairment. The direction of change will depend on the extent and frequency of the damage and on the populations affected. The prevalence rate of impairment is a function of its incidence in the total population, and of the survival of those affected. High incidence combined with low mortality of those impaired would produce the highest prevalence; low incidence and high mortality of the impaired would produce the lowest prevalence.

One possibility is that severely damaged babies who would have died before the advent of neonatal intensive care may now be rescued and contribute to the prevalence of neurological damage. DRILLIEN<sup>1</sup> predicted that as the survival rate for very low-birthweight improved, an increasing number of impaired children would survive. HOLT argued in similar vein<sup>2</sup>, and claimed that many low-birthweight survivors would become a burden on their families and upon society. This is particularly so if neurological handicap arises prenatally<sup>3</sup>. In spina bifida, for example, surgical intervention has been related to increased prevalence, and the cessation of intervention to decreased prevalence<sup>4</sup>.

On the other hand, it is no less likely that the active efforts during recent years to prevent neonatal death among low-birthweight infants have had the opposite result. Profit in the form of undamaged babies may be greater than loss in the form of surviving, severely impaired children who would have died with the less active approach of earlier years. Good care often might shift babies from the impaired to the non-impaired group. At the least, juxtaposition of the available data on mortality and impairment in survivors will show that there must have been a net gain of healthy babies, in spite of any possible increase in the prevalence of neurological impairment.

In Table I we summarize all the hospital studies we could find which provide both mortality and follow-up data for infants weighing < 1500g at birth. The studies are grouped according to the decade of birth of the study infants. Where studies overlap decades, the mid-point of the study is used as the reference point. There is a notable asynchrony in the time trends of prevalence rates of impairment and of newborn mortality. A more than three-fold reduction in the rate of neurological impairment occurred between the 1950s and 1960s, *without* an over-all change in mortality. The next generation of studies showed a slight

\*This is the final part of a three-part annotation. Part I was published in the August issue of the journal and part II in the October issue.

increase in the rate of cerebral palsy among survivors: 8 per cent in the 1970s, compared with 6 per cent in the 1960s. However, in this period of relatively stable rates of cerebral palsy a sharp reduction in mortality had taken place. It follows logically that a constant rate of impairment applied to a steadily increasing proportion of low-birthweight survivors will result in an increase in the over-all prevalence rate of impairment in the population. For this collection of studies, indeed, the prevalence rate of cerebral palsy per 1000 live births in the 1970s appears to be double that for the 1960s. It should be noted, however, that the prevalence rate of the 1970s remains well below the rate of the 1950s.

The high rates of cerebral palsy in the 1950s are open to several interpretations. Perhaps cerebral palsy had always existed at such a rate among low-birthweight babies, but few had survived to swell prevalence rates. Alternatively, such practices of the 1950s as oxygen restriction and late feeding might have contributed to an unusually high incidence. Some evidence favoring the latter interpretation has been proposed by DRILLIEN<sup>5</sup>, who found mental retardation (IQ < 70) in only 6 per cent of a cohort of 1950s births weighing 2000g or less, when those fed late were excluded. Similarly, DOUGLAS and GEAR<sup>6</sup>, finding no unusual rate of neurological impairment among low-birthweight survivors ( $\leq 2000$ g) in the British birth cohort of 1946, concluded that high rates of handicap among low-birthweight infants were a phenomenon of a later period. Inasmuch as studies of the prevalence of cerebral palsy prior to the 1950s are few and far between, it is unlikely that we will ever be able to draw firm conclusions about these rates.

TABLE I  
Cerebral palsy and survival among infants weighing <1500g at birth:  
pooled results from several hospital studies

	1950s studies <sup>9 12*</sup>	1960s studies <sup>13 16</sup>	1970s studies <sup>17 22</sup>
Live births	751	837	1,446
Survivors	280	324	819
Survivors followed up	236	303	744
Cerebral palsy	58	18	60
Survival rate (%)	37.3	38.7	56.6
Prevalence of cerebral palsy per survivors followed up (%)	24.6	5.9	8.1
Prevalence of cerebral palsy per live births (%)**	7.7	2.3	4.6

\* <1360g from Drillien (1978) study; <750g excluded from Wright *et al.* (1971).

\*\* Assuming rate in lost to follow-up same as in followed up.

TABLE II  
Estimated one-year-old survivors from New York City 1976 birth cohort, under two conditions:  
A: birthweight-specific mortality of 1962; B: birthweight-specific mortality of 1976

Birthweights (g)	No. of births	Rate of survival per 1000 live births		Number of survivors		Percent distribution by weight category	
		A	B	A	B	A	B
<1000	707	118	222	84	157	0.08	0.15
1001-1500	882	513	713	453	629	0.42	0.58
1501-2000	2020	832	921	1681	1861	1.57	1.72
>2001	106,386	987	989	105,035	105,256	97.93	97.55
Total	109,995	972	981	107,253	107,903	100.00	100.00

In the light of the questions we have posed, the suspicious rise in the pooled prevalence rates from the 1960s to the 1970s, although smaller than the decline of previous decades, is of greater concern, especially since it occurs simultaneously with a dramatic decline in newborn mortality. Taken together with the experimental and quasi-experimental results reported in the previous section (*DMCN*, 23, 650–659), we cannot know that we are witnessing a decline in prevalence. Caution should be used in interpreting pooled study results, however: we have no assurance that the studies cited are representative of the overall trends in neonatal mortality and morbidity during the eras they are taken to represent. We shall therefore generate estimates of what to expect, given differing mortality and morbidity rates among low-birthweight infants.

*Projected population prevalence rates for neurological impairment*

An increase in the prevalence of neuro-intellectual morbidity can only be avoided if the rate of morbidity declines coincidentally with the decline in mortality. In the rest of this paper, we develop a set of projections for the prevalence of neuro-intellectual morbidity, based on three different assumptions.

The projections take the births in New York City in 1976 as the starting population. In Table II, two sets of birthweight-specific mortality rates are applied to this starting population: A, the rates that pertained in 1962; and B, the rates that pertained in 1976. (These are mortality rates up to the first birthday, made available by the Department of Health, which routinely links birth and infant death certificates.) It can be seen that improving mortality rates had little effect on the size of the population of survivors above 1500g. At lower birthweights, however, the changing pattern of mortality has substantially increased the number of survivors. 1976 rates have resulted in 46 per cent more survivors with birthweights under 1500g than would have been the case had 1962 mortality rates held.

Next, it is necessary to estimate prevalence rates of handicap that would ensue in the population at large under different configurations of mortality and morbidity. The Collaborative Perinatal Project provides the best available estimates of rates of cerebral palsy and severe mental retardation in a US population. In that study, approximately 40,000 infants born between 1959 and 1966 at 12 major medical centers across the country were followed for seven years. Table III presents the prevalence of these handicaps found in that cohort of births\*. Severe mental retardation was almost eight times more common among survivors weighing less than 1500g at birth, compared with normal-birthweight survivors, and cerebral palsy was 24 times more common.

In Tables IV and V we consider three different assumptions:

*Assumption I* is our estimate of the prevalence of impairment *prior* to the era of newborn intensive care. It is based on the mortality rates for 1962 and the morbidity rates found in the Collaborative Perinatal Project (Table III).

*Assumption II* is one estimate of current prevalence of impairment. It assumes that the present (1976) birthweight-specific mortalities prevail, and that the morbidity in survivors has not changed: that is, the impairment rates of the Collaborative Perinatal Project still apply to the now greater number of survivors.

*Assumption III* is a more pessimistic one. It takes current mortality rates, and assumes that the rate of handicap in the *additional* survivors (that is, those now surviving who would have

\*Cerebral palsy rates are derived from published data<sup>7, 8</sup>; mental retardation rates were kindly provided by the National Institute of Neurological and Communicative Diseases and Stroke (J. Ellenberg, Ph.D., Sarah Broman, Ph.D., oral communication, May 1979).

died in 1962) is twice that of the other survivors, who experience the same impairment rates as found in the Collaborative Project.

Table IV shows each of these three assumptions applied to severe mental retardation. Both the number and the proportion of mentally retarded infants deriving from the low-birthweight group increase as we move from Assumption I to Assumption III. Despite these increases, over-all prevalence figures for mental retardation are not much altered, because of the low attributable risk of severe mental retardation in the low-birthweight group.

Table V shows these three assumptions applied to cerebral palsy. The attributable risk of cerebral palsy in infants weighing  $\leq 1500$ g at birth is larger than for mental retardation. Thus, as we move across the table, the excess survivors begin to make up a larger proportion of children with cerebral palsy. Under Assumption III, the number of children with cerebral palsy in the very low-birthweight cohort increases substantially, and the over-all prevalence rate of cerebral palsy among children increases by about 10 per cent.

Some neonatologists believe that the actual prevalence rates of impairment are declining among present-day survivors of intensive care and, as we have noted, at least in some hospital centers there is evidence to support this view. It is simple to calculate, for the given change in mortality among very low-birthweight infants, the decline in rates of morbidity among them which would keep rates of impairment stable in the population at large (Table VI). In order to avoid an increase in the prevalence rates of impairment in the population, the morbidity rates among the low-birthweight must actually decline by 35 to 39 per cent. Severe mental retardation among low-birthweight infants would have to decline from 4.3 to 2.8 per cent and cerebral palsy from 9.4 to 5.7 per cent.

**TABLE III**  
Prevalence rates of neuro-intellectual morbidity at seven years, by birthweight

Birthweight (g)	Severe mental retardation (IQ < 50)	Cerebral palsy
	%	%
< 1500	4.3	9.4
1501-2000	2.1	4.4
> 2000	0.55	0.39
Total	0.60	0.51

Source: Collaborative Perinatal Project (see text).

**TABLE V**  
Number of cases and prevalence rates of cerebral palsy by birthweight, estimated on three separate assumptions applied to New York City births, 1976.

Birthweight (g)	Assumption I		Assumption II		Assumption III	
	No.	%	No.	%	No.	%
$\leq 1500$	50	9.4	74	13.1	97	16.2
1501-2000	74	13.9	82	14.5	90	15.1
$\geq 2000$	410	76.8	410	72.4	411	68.7
Total	534	100.0	566	100.0	598	100.0
Rate per 1000	5.0		5.2		5.5	

ASSUMPTIONS: see footnote to Table IV.

**TABLE IV**  
Number of cases and prevalence rates of mental retardation by birthweight, estimated on three separate assumptions applied to New York City births, 1976

Birthweight (g)	Assumption I		Assumption II		Assumption III	
	No.	%	No.	%	No.	%
$\leq 1500$	23	3.6	34	5.2	44	6.6
1501-2000	35	5.5	39	6.0	43	6.4
$\geq 2000$	578	90.9	579	88.8	580	87.0
Total	636	100.0	652	100.0	667	100.0
Rate per 1000 survivors	5.9		6.0		6.2	

**ASSUMPTIONS:**

- I. That in New York City in 1976, birthweight-specific survival rates for 1962 and morbidity rates of the Collaborative Perinatal Project apply (see text).
- II. That in New York City in 1976, current birthweight-specific survival rates and birthweight-specific morbidity rates of the Collaborative Perinatal Project apply.
- III. That in New York City in 1976, current birthweight-specific survival rates apply, but that those who would have died and now survive have twice the birthweight-specific morbidity rates expected from the Collaborative Perinatal Project.

TABLE VI  
 Decline in morbidity rate needed to prevent  
 increase in population prevalence of brain  
 disorders following decline in mortality rate  
 for very low-birthweight infants\*

	1962	1976	% decline
Infant mortality rate < 1500g (%)	66·2	50·5	23·7
Mental retardation prevalence rates	0·043	0·028	35·1
Cerebral palsy prevalence rates	0·094	0·057	39·2

\*Assuming constant number and birthweight distribution of births.

### Conclusions

No doubt many neonatologists would consider our assumptions unduly pessimistic; nonetheless, they are instructive. The prevalence rates for cerebral palsy and mental retardation in the population are sensitive to changes in the probability of survival among infants of very low birthweight. Given rapidly declining mortality, which may well continue further than was noted in New York City in 1976, the morbidity rate among very low-birthweight survivors must be reduced substantially merely to avoid contributing to an increase in the handicap rate in the population. This observation leads inevitably to the conclusion that intensive medical effort to save the lives of low-birthweight newborns can have beneficial effects on prevalence rates of impairment in the population only if the impairment rate among low-birthweight survivors declines more rapidly than does their neonatal mortality rate.

In these three annotations we have reviewed the available evidence on both sides of this balance. The evidence that the mortality rate is declining for low-birthweight infants, both in hospitals and in populations, is more convincing than the evidence that the rates for cerebral palsy or other impairments are declining. Studies since the early 1960s show a fairly stable, if not an increasing, prevalence rate for cerebral palsy of between 6 and 9 per cent among survivors weighing less than 1500g at birth. However, these same studies show consistently improving mortality rates over time. Thus the limited evidence we have so far suggests that neonatal intensive care is quite likely to be associated with a modest net increase in the prevalence rates for cerebral palsy.

This observation must be tempered by several reservations. In the first place, data on neurological impairment necessarily are less exact than mortality data, and we do not yet know the rates of impairment associated with newborn care as it is practised now. Secondly, even our most pessimistic projections call for an increase of only 10 per cent in cerebral palsy prevalence, and of 5 per cent in mental retardation. These potential increases in the prevalence rates of impairment must be weighed against the parallel increases in surviving healthy children. In New York City in 1976, for each 1000 live births weighing 1500g or less, 157 children who would have succumbed in 1962 survived the first year of life. Clearly the majority of these children are developmentally intact. A strong argument can be mounted that this net gain offsets the modest increase in the prevalence rate of neurological impairment.

The analysis of available data leaves us with a number of tentative conclusions for

developed countries, particularly for Britain and the United States.

(1) Changes from the 1950s to the 1960s seem to have led to a sharp reduction in the frequency of neurological impairment in low-birthweight infants. The operative factor may have been technical change in newborn care; if so, it left neonatal mortality almost untouched.

(2) Changes from the 1960s to the 1970s led to a sharp reduction in neonatal mortality, and probably to a moderate rise in the prevalence of neurological impairment. The operative factor is very likely to have been technical advance in newborn care.

To clarify these issues, questions have still to be answered. The most urgent seem to us to be the following:

What are the *current* prevalence rates of neurological impairment in infants exposed to different forms and intensities of newborn care?

What contemporary techniques of perinatal care for the newborn influence the frequency of subsequent neurological impairment?

What are the attributes of newborn infants treated by the best of contemporary techniques that point to a good or poor prognosis for subsequent neurological impairment?

### Summary

To maintain a stable over-all prevalence of handicap, the rate of handicap among survivors must decline in parallel to the decline in mortality among live births. The 24 per cent decline in mortality among low-birthweight infants in New York City between 1962 and 1976 requires a 35 to 39 per cent decline in the rate of neurological impairment among low-birthweight survivors simply to avoid the production of an increased number of handicapped children in the population as a whole.

Such evidence as we have suggests that the declining morbidity may not be keeping pace with the recent declines in mortality: thus, although more healthy survivors will result from newborn intensive care, a modest increase in the prevalence of handicap may also ensue.

The Gertrude H. Sergievsky Center,  
The School for Public Health and the  
Department of Pediatrics, Columbia University,  
630 West 168th Street, New York, New York 10032.

NIGEL PANETH\*  
JOHN L. KIELY  
ZENA STEIN\*  
MERVYN SUSSER

\*and New York State Psychiatric Institute,  
722 West 168th Street, New York, New York 10032.

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## VIRUS INFECTIONS OF THE CENTRAL NERVOUS SYSTEM IN CHILDREN WITH PRIMARY IMMUNE DEFICIENCY DISORDERS

BOYS with infantile or sex-linked hypogammaglobulinaemia are subject to recurrent bacterial infections which begin within the first two years of life and respond well to regular gammaglobulin injections. Before or after the start of gammaglobulin therapy these patients resist viral infections normally, with the notable exceptions of echovirus and vaccine-poliovirus. Children with hypogammaglobulinaemia and chronic echovirus infections have been described by several authors<sup>1-5</sup>. In a typical case, chronic meningoencephalitis is associated with chronic myositis, but either may occur alone. A slowly progressive or relapsing-remitting course is seen, with headaches, convulsions,