CEREBRAL PALSY AND NEUROLOGICAL IMPAIRMENT IN
LOW-BIRTHWEIGHT INFANTS

In a companion paper (DMCN, 23, 533-538), we reviewed time trends in the occurrence of cerebral palsy in industrialized countries. We concluded that the evidence did not support the notion of a steady decline in cerebral palsy, nor a trend that can be attributed to the operation of the single factor of newborn care.

The association of cerebral palsy with an array of perinatal conditions is well established; low birthweight and preterm gestation are among the strongest risk factors for motor handicap, and metabolic abnormalities such as hypoxia and hyperbilirubinemia add to the risk. Moreover, there has been a remarkable acceleration in the rate of innovation in fetal and newborn medicine over the last two decades in many industrialized nations, much of it centered on the clinical management of sick low-birthweight infants. Because these innovations might influence mortality, as well as impairment among survivors, in this second paper we examine each of these outcomes in turn, and weigh the contribution to them of newborn care.

Hospital data

The evidence that active neonatal care has reduced mortality in low-birthweight infants is plausible and convincing. Favorable time trends in neonatal mortality by birthweight have been reported from several hospitals which have adopted modern methods of neonatal intensive care. Over-all, the decreases in neonatal mortality, especially among babies weighing under 2000g, tend to be sizeable and consistent, although the magnitude of the improvement varies considerably from hospital to hospital. These results cannot be generalized to populations because of the selective and variable nature of hospital admissions. The results of some typical studies are presented in Figure 1, and the most recent reports show even sharper declines than shown in Figure 1.

Population data

The birthweight of neonates who die, while frequently recorded in hospitals, is seldom ascertained for the population at large. Therefore it is difficult to assess the rate, or even the presence, of a decline in mortality for low-birthweight infants in the total population. In the United Kingdom, birthweight is recorded for deaths in all infants weighing <2500g at birth. Between 1953 and 1971, a definite decline in mortality was noted for low-birthweight infants, which was greatest in deaths between one and 28 days among infants weighing 1500

*This is part II of a three-part annotation: part III will be published in the December issue of the journal.
to 2500g at birth. In this category, 1971 mortality was approximately 50 per cent of 1953 mortality. Although the reliability of the weights recorded on spring scales at home deliveries could be questioned, this should not seriously affect such time trends. Pharoah and Alberman confirm that the decline is continuing.

In the United States, the linkage of infant birth and death certificates is some States has facilitated mortality analysis by birthweight. During the 1960s, declining rates were noted in all weight groups under 2500g in New York City and in Oklahoma, Rhode Island, Utah, Vermont and Washington State. When analyzing over-all neonatal mortality, it must be remembered that birthweight is by far the most powerful factor in such mortality; and before other factors can be weighed, changes in mortality associated with changes in birthweight distribution need to be examined. Kleinman et al. attributed 21 per cent of the over-all decline in mortality in their study of five States to changes in birthweight, leaving 79 per cent attributable to mortality changes within birthweight groups. Lee et al. have pointed out that the decline in neonatal mortality rates in the US as a whole between 1950 and 1975 occurred without benefit of improvement in the weight distribution of live births during that period. Average weight-specific mortality (over all birthweight groups) was estimated to be 40 per cent lower in 1975 than in 1950. The same authors have recently found a similar pattern in Canada.

Figure 2 shows that in the period 1960 to 1975, low-birthweight infants in several populations in the United States, Great Britain and Canada experienced declines in neonatal mortality rates. From these data, it seems safe to conclude that there have been general declines in the industrialized world. It is a reasonable and strong assumption, but one still to be proven, that the trends in mortality can be attributed to improvements in the quality of perinatal care. We turn now to consider what evidence can be mustered about the effects of the quality of newborn care on prevalence rates of neurological handicap among survivors. A priori, one could sustain an argument for a change in either direction.

Neurological impairment and neonatal care in hospital series

The available evidence on the effects of highly-specialized medical care for the newborn does not lead to definite conclusions about outcome in surviving very low-birthweight children. Several of these studies are summarized in Tables I and II, in which the variation in rates of handicap can be seen.

The disparate results among hospital studies must arise, at least in part, from differences in the character and experiences of the study populations. For example, 48 per cent of the infants in the investigation of Stewart et al. were transferred from other hospitals; 100 per cent of the babies in the Toronto study of Fitzhardinge et al. were 'transferred in'; and in several other studies the data on transfers are not given. All 'transferred-in' newborns have experienced the stress of transport, and some of them also have had sub-optimal initial care. In some situations 'transferred-in' babies will be the sickest of the low-birthweight cohort, in others they must be hardy survivors if they are to arrive intact at the new location. Different proportions of 'transferred-in' babies, exposed to different kinds of transport processes, can be expected to produce different results.

Comparison is further complicated by the ways in which outcome is measured and reported. The types of tests used, and the ages at which they are applied, follow no standard conventions. Confounding factors correlated with the tests, for instance social class and parental education, are often left uncontrolled and permit no inference to be drawn.
Fig. 1. Time trends in mortality rates for birthweight categories under 2000g in several high-risk centers (deaths per 1000 live births in each category). Data sources: Washington D.C.: Erkan et al.; Philadelphia: Kendall; San Francisco and Texas: Schlesinger; London: Stewart and Reynolds; Bronx, N. Y.: Lee et al.; Baltimore: Schaffer and Avery.

Fig. 2. Neonatal mortality for infants with birthweights 1000 to 1500g in several populations. Data sources: Five States and North Carolina: Kleinman et al.; New York City: Pakter and Nelson; England and Wales: Alberman; Province of Quebec: Usher; Bradford, England: Congdon and Lealman.
TABLE I
Survival, neurological impairment and mental retardation among children with birthweights <1001g: some recent studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Years of birth</th>
<th>Live births</th>
<th>Survivors</th>
<th>Survivors followed up</th>
<th>Cerebral palsy</th>
<th>Mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alden et al.41</td>
<td>University of Washington Hospital, Seattle</td>
<td>1965-70</td>
<td>161</td>
<td>12 (20)</td>
<td>100 (20)</td>
<td>5 (1)</td>
<td>40 (2) DQ &lt;70</td>
</tr>
<tr>
<td>Dweck et al.42</td>
<td>University of Alabama, Birmingham</td>
<td>1968-70</td>
<td>82</td>
<td>18 (15)</td>
<td>93 (14)</td>
<td>14 (2)*</td>
<td>7 (1) DQ &lt;80</td>
</tr>
<tr>
<td>Grassy et al.43</td>
<td>Regional NICU, Madison, Wis.</td>
<td>1968-72</td>
<td>98</td>
<td>28 (27)</td>
<td>100 (27)</td>
<td>7 (2)</td>
<td>14 (4) Delayed development</td>
</tr>
<tr>
<td>Stewart and Reynolds44</td>
<td>University College Hospital, London</td>
<td>1966-75</td>
<td>148</td>
<td>26 (39)</td>
<td>69 (27)</td>
<td>4 (1)</td>
<td>12 (1) Severe MR</td>
</tr>
<tr>
<td>Bhat et al.45</td>
<td>University of Illinois, Chicago</td>
<td>1974-76</td>
<td>100</td>
<td>23 (23)</td>
<td>70 (16)</td>
<td>19 (3)*</td>
<td>19 (3) DQ &lt;85</td>
</tr>
<tr>
<td>Pape et al.46</td>
<td>Hospital for Sick Children, Toronto</td>
<td>1974</td>
<td>97</td>
<td>46 (45)</td>
<td>96 (43)</td>
<td>9 (4)</td>
<td>27 (4) DQ &lt;50</td>
</tr>
<tr>
<td>Pomerance et al.47</td>
<td>Cedars-Sinai Medical Center, Los Angeles</td>
<td>1973-75</td>
<td>75</td>
<td>40 (30)</td>
<td>90 (27)</td>
<td>15 (4)*</td>
<td>30 (4) DQ &lt;40</td>
</tr>
<tr>
<td>Bethenod et al.48</td>
<td>Hopital Debrousse, Lyon, France</td>
<td>1967-76</td>
<td>139</td>
<td>29 (40)</td>
<td>78 (31)</td>
<td>12 (4)</td>
<td>18 (4) DQ &lt;75</td>
</tr>
<tr>
<td>Driscoll et al.49</td>
<td>Columbia-Presbyterian Medical Center, N.Y.</td>
<td>1978</td>
<td>54</td>
<td>44 (24)</td>
<td>96 (23)</td>
<td>9 (2)</td>
<td>31 (4) Clearly abnormal</td>
</tr>
</tbody>
</table>

*Includes all children classified as ‘moderately to severely abnormal’ according to neurological examinations.
**Includes all liveborn infants with birthweights up to 1100g.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Years of birth</th>
<th>No. of births</th>
<th>Survivors followed up</th>
<th>Survivors</th>
<th>Survivors with cerebral palsy</th>
<th>Survivors with mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calame and Proctor</td>
<td>University of Lausanne, Switzerland</td>
<td>1966-68</td>
<td>185</td>
<td>36 (66)</td>
<td>86 (57)</td>
<td>2 (1)</td>
<td>28 (1)</td>
</tr>
<tr>
<td>Drellen</td>
<td>Simpson Memorial Pavilion, Edinburgh</td>
<td>1966-71</td>
<td>251</td>
<td>37 (93)</td>
<td>95 (88)</td>
<td>8 (7)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Homers &amp; Co.</td>
<td>Coventry Maternity Hospital, England</td>
<td>1973-74</td>
<td>103</td>
<td>42 (43)</td>
<td>98 (42)</td>
<td>2 (1)</td>
<td>10 (2)</td>
</tr>
<tr>
<td>Kendall et al.</td>
<td>Women's Hospital, Sydney, Australia</td>
<td>1971-73</td>
<td>155</td>
<td>50 (78)</td>
<td>74 (58)</td>
<td>7 (4)</td>
<td>5 (3)</td>
</tr>
<tr>
<td>Black et al.</td>
<td>Sydney Children's Hospital, Australia</td>
<td>1974</td>
<td>250</td>
<td>67 (64)</td>
<td>91 (149)</td>
<td>9 (13)</td>
<td>27 (40)</td>
</tr>
<tr>
<td>Fitzhardinge et al.</td>
<td>Children's Hospital, London</td>
<td>1975</td>
<td>161</td>
<td>71 (114)</td>
<td>78 (89)</td>
<td>12 (11)</td>
<td>13 (12)</td>
</tr>
<tr>
<td>Kepos</td>
<td>Royal Hospital, Sydney</td>
<td>1971-75</td>
<td>188</td>
<td>53 (100)</td>
<td>88 (88)</td>
<td>2 (2)</td>
<td>8 (8)</td>
</tr>
<tr>
<td>Mercer et al.</td>
<td>Australia</td>
<td>1961-75</td>
<td>357</td>
<td>40 (143)</td>
<td>97 (138)</td>
<td>5 (7)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>Jones et al.</td>
<td>HamnerSmith Hospital, University College, London</td>
<td>1966-76</td>
<td>589</td>
<td>54 (320)</td>
<td>99 (318)</td>
<td>6 (29)</td>
<td></td>
</tr>
</tbody>
</table>

*Includes all cases of 'severe handicap,' since cerebral palsy was not reported separately.
**Estimated from survival rates of very low-birthweight infants delivered in Simpson Memorial Pavilion.

TABLE 11 Survival, neurological impairment and mental retardation among children with birthweights < 1500 g: some recent studies.
Whether or not assessments were carried out blind and protected from subjective observer bias is often not reported.

Among the most favorable reports are those from University College Hospital, London. STEWART and her co-workers, in several papers on the development of low-birthweight survivors from their neonatal intensive care unit at University College Hospital, find the current prognosis to be excellent. Between 1966 and 1976, survival through the first month of life among 589 babies with birthweights between 500 and 1500g was 60 per cent27. This is a higher survival rate than in most hospitals in England during that period29. In 1977, survival for inborn infants weighing 1000 to 1500g was reported to be a remarkable 93 per cent10.

The mental competence and neurological status of 318 of those children who weighed less than 1500g at birth were assessed at ages ranging from 18 months to eight years30. They comprised 99 per cent of survivors. Only 9 per cent were classified as handicapped. STEWART et al.31 also reported on 27 children who weighed under 1000g at birth. They comprised 69 per cent of survivors, and neonatal survival was 32 per cent among those born alive between 1966 and 1975. Major handicaps were found in only two of these children (one was severely mentally retarded with cerebral palsy and the other was partially sighted as a result of congenital cataracts), and minor handicaps were found in another four (15 per cent).

Others report less striking improvement. An intermediate result is that of CALAME and PROD'HOM in Switzerland32. They studied 185 premature babies with birthweights of 1500g or less in the period 1966 to 1968, of whom 66 (36 per cent) survived to 1972. Of the 57 children followed up, 11 per cent had clearly abnormal development, and the development of another 14 per cent was classified as 'doubtful'. A pessimistic result is that of FITZHARDINGE et al. from Canada28: of 149 surviving infants weighing <1500g at birth and examined two years later, 30 per cent had either major neurological defects or low scores on Bayley developmental testing.

Other follow-up series of 'high risk' infants are summarized in Tables I and II. The median rate of cerebral palsy in survivors is about 7 per cent. The median rate of mental retardation (including borderline IQs), is about 15 per cent in the nine studies of preschool children listed in Table II. It is clear that the very low-birthweight infant remains at substantial, if much reduced, risk of mortality, and also continues to have substantial risk of neurological impairment.

The optimism generated by these reports stems mainly from the background against which many of their authors place them. Studies by DRILLIEN33 and by LUBCHENCO et al.34 of babies born in the 1950s, prior to the era of newborn intensive care, showed very high rates of cerebral palsy and other forms of impairment in survivors. However, not all reports from that era are so uniformly pessimistic. In the Collaborative Perinatal Project, which ran from 1959 to 1966, and thus for the most part predates newborn intensive care, the rate of cerebral palsy for infants <1500g at birth was 9 per cent35, not very different from the median rate in Table II. Similarly, ALISON MCDONALD, reporting on infants born between 1951 and 1953, found a cerebral palsy rate of 6·5 per cent among children weighing <1800g at birth1.

The nature of the hospital series gathered in Tables I and II, with their selected populations, and particularly their lack of controls, makes it difficult to use them as a source for understanding the likely effect of newborn care on the prevalence of handicap in the population.

Three studies, in principle, allow for much stronger inference: these take advantage of
simultaneous comparisons to examine mortality and subsequent development in relation to newborn care. In one quasi-experimental study, PHAROAH investigated the outcome in 244 children weighing <2500g at birth. They were born in 1966 in two hospitals with differing neonatal mortality rates: in one the neonatal mortality rate for babies weighing less than 2500g was 106 per 1000, in the other the rate was 161 per 1000 live births. At age six, the survivors from the two hospitals did not differ significantly in the prevalence of either mild or severe mental handicap. However, they did differ in the prevalence of cerebral palsy: rates were higher in the hospital with the superior rescue rate (4 per cent vs 1 per cent). However, with the small numbers involved, the study lacked the power to confer statistical significance on this level of difference.

More recently, STEINER et al. reported results from King's Mill Hospital, Mansfield, England, from 1963 to 1971; in that unit standards of newborn nursing care were high, but medical intervention was avoided. The authors compared outcome in school-age children of 501-1500g birthweight born at King's Mill with the results found in survivors of the newborn intensive care unit at Hammersmith Hospital, apparently using the same definitions of live birth, social class, intra-uterine growth retardation, handicap and cognitive function. Results from the two units were strikingly similar. This study seems to show that, once survival was secured, intensive care did not influence rates of neurological impairment, either favorably or unfavorably.

The third study, conducted in Australia, had an experimental design. The results obtained were in some respects similar to those of PHAROAH. In a controlled clinical trial, KITCHEN et al. investigated the outcome at age eight in 153 children who had weighed between 1000 and 1500g at birth. Children from the Royal Women's Hospital in Melbourne born between 1966 and 1970 had been randomly allotted either to neonatal intensive care or to routine care. In the intensive-care group the mortality rate was 29 per cent; in the routine-care group it was 38 per cent. The overall prevalence of profound and serious impairment among children who survived the neonatal period was higher in the intensive-care group than in the routine-care group (20 per cent vs 8 per cent), a difference of borderline statistical significance (p = 0.0518). With particular regard to cerebral palsy, however, the rate was lower in the intensive-care group (1 per cent vs 5.5 per cent), in contrast with PHAROAH'S result. KITCHEN et al. concluded that newborn intensive care achieved the reduced neonatal mortality at the expense of adding to the numbers of severely handicapped children (but not of those with cerebral palsy).

Thus no consistent pattern emerges from studies of the effect of newborn intensive care on neurological impairment in survivors. Present-day rates of impairment are lower than were found in some, but not all, studies that predate the era of newborn intensive care. The most significant finding, however, is the recent sharp decline in mortality for low-birthweight infants, which is of sufficient magnitude to affect population statistics on neonatal mortality. This change, which substantially increases the number of low-birthweight survivors, and especially of infants in the very lowest birthweight categories, is the most striking result of newborn intensive care. As we will point out in our third paper, no consideration of the net effect of newborn intensive care on handicap in the population can ignore this important demographic shift.

Summary

In recent years, neonatal mortality rates for low-birthweight infants have declined both in neonatal intensive care units and in several populations in the industrialized world. With
regard to impairment among surviving low-birthweight infants, studies from newborn intensive care units show considerable variation in the reported rates of handicaps. Much of this variation arises from a lack of uniform criteria for diagnosis, sample selection and follow-up, factors further compounded by small sample size. At the present time it is premature to conclude that changes in newborn care have either lowered or raised rates of impairment among surviving low-birthweight infants.

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658


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