Improved Prognosis for Infants of Very Low Birthweight


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ABSTRACT. Following the introduction of a program of intensive care for infants of very low birthweight, 197 infants who weighed 1,500 gm or less at birth were cared for in the Neonatal Unit of University College Hospital, London, in the five years from 1966 to 1970. During this period, the neonatal survival rate for infants weighing 501 to 1,000 gm was 23% and for those weighing 1,001 to 1,500 gm was 69%. The principal immediate cause of death was hypoxia around the time of birth or hyaline membrane disease. Ninety-five of the 98 surviving children, aged 2 years 10 months to 7 years 10 months (mean, 5 years 2 months) were followed up. They all had repeated physical examinations and developmental assessments. Sixty-five of the older children also had IQ tests. The results showed that 86 (90.5%) of the children had no detectable handicap, 4 (4.2%) had physical handicaps only, and 5 (5.3%) had mental handicaps, including two children with physical handicaps. The incidence of handicap was very much greater among infants presumed to have been severely hypoxic than among the remaining infants.

We conclude that intensive care can both increase the chance of survival for infants of very low birthweight and reduce the incidence of serious handicap in survivors. Pediatrics, 54:724, 1974, LOW BIRTHWEIGHT, NEWBORN, INTENSIVE CARE, PROGNOSIS, INTENSIVE CARE.

Increasing knowledge of how to manage seriously ill newborn infants has been followed by the establishment of intensive care nurseries in many large hospitals. While these nurseries undoubtedly save more lives than less highly developed units, there is concern about the mental and physical well-being of the survivors. In the past, low-birthweight infants, who form the largest group requiring intensive care, have had a poor prognosis for normal development. The smaller the infant, the worse the outlook; for example, Drillien found that 83% of infants weighing less than 1,250 gm at birth proved abnormal at follow-up. Drillien and more recently Holt have suggested that measures taken to increase the survival rate of infants of very low birthweight would result in an increasing number of handicapped children entering the community, where they would become a burden on their families and upon society. While not all have taken such a dismal view of the efficacy of perinatal intensive care, those looking after the smallest infants have been faced with a dilemma similar to that which relates to the management of infants with severe congenital malformations: is it worthwhile using sophisticated methods of treatment to preserve life if the ultimate prognosis is so questionable?

In order to obtain information on this point, a follow-up study of infants weighing 1,500 gm or less at birth was started in our hospital at the beginning of 1966, after the introduction of an intensive care program which was designed to foresee and prevent, as well as treat, any abnormality which might be lethal or damage the infant. An increase in survival rate followed and in 1971 a preliminary report on the progress of the infants was published showing that most appeared to be developing normally. At that time, the number of infants under surveillance was small and they were still very young. The purpose of the present report is to describe the outcome for all infants weighing 1,500 gm or less born in our hospital or admitted to the neonatal unit from other institutions during the five-year period from 1966 to 1970 inclusive. The surviving infants are now aged 2 years 10 months to 7 years 10 months, old enough for the identification of those who have handicaps which will prevent them from func-
tioning as normal individuals in society.\textsuperscript{3} In order to delineate areas where improvements of care are required, details of all infants who died are included, and the methods of perinatal management which were employed are described. Where infants have been found to have an abnormality at follow-up, a relationship with perinatal events has been sought.

**MATERIALS AND METHODS**

**Study Population**

During the five-year period from 1966 to 1970, 123 live-born infants who weighed 1,500 gm or less at birth were born in University College Hospital (UCH). An infant was classified as live-born if any cardiac or respiratory activity was detected after delivery. Another 74 infants were admitted from 19 hospitals situated over a wide area in and around London. Criteria used by these hospitals to decide upon the transfer of a particular infant in addition to the very low birthweight are not known, but because of the special interest of the staff of the neonatal unit are likely to have included the presence of respiratory illness.

**Obstetric Care at UCH**

The condition of the infants who were growing poorly in utero was checked by means of hormone assays such as maternal urinary estriol excretion and by ultrasonic biparietal diameter measurements. The optimum time for the delivery of fetuses who were at risk in utero was decided after consultation between obstetricians and pediatricians. Women admitted in preterm labor were treated with bed rest, sedation, and drugs such as isoxuprine in an attempt to prevent delivery. If labor continued, the fetal heart rate was repeatedly checked, often using an ultrasonic fetal heart detector. Fetal blood samples were taken\textsuperscript{4} when indicated for measurement of acid-base status, and continuous heart rate monitoring was used in a few infants towards the end of the five-year period. Forceps were often applied during delivery in order to protect the head. Breech deliveries were conducted as rapidly as was consistent with safety, in order to avoid asphyxia during umbilical cord compression.

Women booked for delivery in other hospitals which did not have facilities for neonatal intensive care were, if they went into preterm labor and if their obstetricians requested it, transferred to UCH for delivery.

**Neonatal Care**

Because the infants were under the care of the same senior medical and nursing staff throughout the period of study, uniformity of care was assured.

**Resuscitation at Birth**—Pediatricians were warned in advance of the delivery of a low-birthweight infant and were present in the delivery room. Every effort was made to prevent hypoxia. After birth the infant was kept warm and the airway was cleared: if no respiratory efforts were made, the heart rate was below 80 beats per minute, and there was little or no tone, endotracheal intubation was carried out. The lungs were held inflated with oxygen at a transpulmonary pressure of 30 cm of H\textsubscript{2}O for several seconds and then rhythmically inflated at a frequency of about 40 per minute to a pressure sufficient to produce adequate chest movement, usually about 15 cm of H\textsubscript{2}O. When the infant's condition did not rapidly improve, 2 to 5 ml of 5\% sodium bicarbonate solution were injected slowly into the umbilical vein. External cardiac massage was used in infants with a very slow heart rate and nalorphine (0.25 mg) was injected intravenously when an infant whose mother had had a substantial amount of opiate analgesia was slow to breathe. Endotracheal tubes were often left in situ until the infant arrived in the neonatal unit, which was very close to the delivery room, so that breathing could be further assisted if necessary.

**Transfer of Infants**—Infants transferred from other hospitals were almost always collected in a portable incubator by a member of the medical or nursing staff trained in resuscitation. Before and during the journey steps were taken to ensure that the infant was properly warmed and oxygenated. The blood glucose level was usually checked with Dextrostix\textsuperscript{*} and oral or intravenous glucose solution was given if indicated. When the history and clinical state of the infant suggested severe acidosis, small intravenous doses of 5\% sodium bicarbonate solution were also given. Infants who were apneic or whose breathing appeared very precarious were intubated so that intermittent positive pressure ventilation could be used in transit. Since early 1968 the portable incubator has been equipped with a mechanical ventilator in order to facilitate the transfer of apneic infants.\textsuperscript{10}

**Temperature Control**—The infants were nursed in incubators and maintained in the neutral thermal range.\textsuperscript{11} They were moved into cots when they had reached a conceptual age of about 34 weeks or a weight of about 1,800 gm.

**Hydration and Feeding**—Fine nasogastric feeding tubes were passed as soon as possible after ad-

mission and feeding was started, usually with human milk obtained from the infant's mother. The smallest and ill infant were given small amounts of milk every five or ten minutes, and the more robust ones were fed hourly. As the infants grew the intervals between feedings were increased. At about 10 days cow's milk formula feeding was introduced for most infants. The nasogastric tubes were changed to the other nostril weekly. For the first few days of life when the total fluid requirement was not tolerated orally, a parenteral infusion of 10% dextrose with electrolytes was also provided. Umbilical venous catheters were often used during 1966 but subsequently the infusions were given either through an umbilical artery catheter or a peripheral vein. The total fluid administered to the infant on the first day of life was about 65 ml/kg/24 hr and the volume was increased to 150 ml/kg/24 hr by the 7th to 10th days. An attempt was made to raise the caloric intake to 100 calories/kg/24 hr or more by the 7th to 10th days. Bottle-feeding was instituted as soon as the infant could suck adequately.

**Oxygen Therapy**—Measurement of arterial oxygen tension, carbon dioxide tension, and pH were made within two hours of birth, and subsequently as indicated in almost all the infants. Arterial samples were obtained from indwelling umbilical artery catheters or by percutaneous puncture of peripheral arteries, and the estimations were performed on equipment present in the unit. The inspired oxygen concentration was measured with oxygen analyzers and regulated to produce an arterial oxygen tension (Pao2) in the range of 50 to 90 mm Hg. Umbilical artery catheters were removed at 48 hours or sooner, except in a few infants with severe hyaline membrane disease when they were left in place for up to five days. Peripheral artery sampling often continued for several weeks. Metabolic acidosis was totally or partially corrected by intravenous injections of 5% sodium bicarbonate solution (600 mM/liter) and infusions of hypotonic sodium bicarbonate solution (100 mM/liter). We aimed to correct a base excess less than about -6 mEq/liter to 0 in the smallest, ill infants, particularly if they had severe respiratory problems. If the infant was asymptomatic, however, a metabolic acidosis of this or sometimes greater severity was often not treated.

**Monitoring and Management of Apneic Attacks**—In the early years cardiac ratemeters were used for monitoring, and cardiac slowing was the signal employed to detect apnea. In 1968 impedance pneumographs were sometimes used and in 1969 apnea alarm mattresses were introduced. After that time all infants were monitored with apnea alarm mattresses set to detect apnea after a delay of 5 to 15 seconds and cardiac ratemeters were frequently used as well. The nursing staff carefully observed the infants and in the event of apneic attacks stimulated them to breathe by maneuvers such as flicking the sole of the foot. If breathing did not rapidly resume, the lungs were inflated with oxygen. Systems using bags and masks were used intermittently as a substitute for intubation, but were not generally accepted because they were less effective in rapidly overcoming hypoxia, and distension of the stomach with vomiting was sometimes provoked. As soon as an intubated child resumed breathing the endotracheal tube was removed. If breathing remained inadequate he was mechanically ventilated. Since 1968 some infants have had their arterial blood pressure monitored by attaching a strain-gauge transducer to an umbilical artery catheter.

**Mechanical Ventilation**—The indications for using mechanical ventilation, which was needed principally for hyaline membrane disease, were very strict. Initially the only indications were apnea or a deterioration in clinical condition accompanied by peripheral vasoconstriction, bradycardia, or gasps superimposed on a slowing respiratory frequency. More recently, since mid-1969, we have also ventilated infants whose Pao2 fell below 35 mm Hg while they were breathing a concentration of oxygen greater than 95%. The ventilator usually employed was the Bennett PR2. Details of our ventilator management have been given elsewhere. The only important change which occurred during the years 1966 to 1970 was that at the end of 1969 means were found to ventilate infants with hyaline membrane disease at much lower peak airway pressures than we had previously used and it also became possible to ventilate some of them with lower concentrations of oxygen.

**Management of Hypoglycemia, Jaundice, and Hypocalcemia**—Blood glucose levels were measured in all infants using Dextrostix. Laboratory determinations were made when indicated. Enough extra oral or intravascular glucose was given to maintain the blood glucose level above the lower limit of detection with Dextrostix (initially 40 mg/100 ml, later 25 mg/100 ml). Bilirubin measurements were made in all jaundiced infants. The level of indirect-acting bilirubin which was regarded as an indication for exchange transfusion was lowered somewhat as the five-year period progressed. For example, at 28 weeks of gestation.
TABLE I
TWENTY-EIGHT-DAY SURVIVAL RATE BY BIRTHWEIGHT OF 197 INFANTS BORN IN 1966 TO 1970

<table>
<thead>
<tr>
<th>Birthweight (gm)</th>
<th>UCH</th>
<th></th>
<th>Outborn</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live</td>
<td>Dead</td>
<td>Survived</td>
<td></td>
<td>Live</td>
<td>Dead</td>
</tr>
<tr>
<td>501-750</td>
<td>0</td>
<td>14</td>
<td>0</td>
<td></td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>751-1,000</td>
<td>7</td>
<td>15</td>
<td>32</td>
<td></td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>1,001-1,250</td>
<td>24</td>
<td>15</td>
<td>61</td>
<td></td>
<td>14</td>
<td>8</td>
</tr>
<tr>
<td>1,251-1,500</td>
<td>36</td>
<td>12</td>
<td>75</td>
<td></td>
<td>21</td>
<td>7</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>56</td>
<td>54</td>
<td></td>
<td>42</td>
<td>32</td>
</tr>
</tbody>
</table>

TABLE II
TWENTY-EIGHT-DAY SURVIVAL RATES BY GESTATIONAL AGE OF 197 INFANTS BORN FROM 1966 TO 1970

<table>
<thead>
<tr>
<th>Gestation (Completed Weeks)</th>
<th>UCH</th>
<th></th>
<th>Outborn</th>
<th></th>
<th>Total</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Live</td>
<td>Dead</td>
<td>Survived</td>
<td></td>
<td>Live</td>
<td>Dead</td>
</tr>
<tr>
<td>&lt;24</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>24-25</td>
<td>0</td>
<td>10</td>
<td>0</td>
<td></td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>26-27</td>
<td>5</td>
<td>14</td>
<td>26</td>
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<td>3</td>
<td>5</td>
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<td>28-29</td>
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<td>17</td>
<td>48</td>
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<td>11</td>
<td>10</td>
</tr>
<tr>
<td>30-31</td>
<td>23</td>
<td>6</td>
<td>79</td>
<td></td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>32-33</td>
<td>13</td>
<td>4</td>
<td>76</td>
<td></td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>34-40</td>
<td>10</td>
<td>1</td>
<td>91</td>
<td></td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>56</td>
<td>54</td>
<td></td>
<td>42</td>
<td>32</td>
</tr>
</tbody>
</table>

*The length of gestation was assessed from the date of the mother's last menstrual period and from the neurological and physical characteristics of the infant.

Table: Baby's birthweight and survival rate.

Mechanical ventilation was used for children with severe hyaline membrane disease. A level below 17 to 18 mg/100 ml was considered safe in 1966, whereas in 1970 we sometimes performed exchange transfusions to prevent the level reaching 15 to 16 mg/100 ml, particularly if the infant had severe hyaline membrane disease, or a tendency to apnea. Towards the end of the period phototherapy and occasionally phenobarbital were used to control jaundice. The plasma calcium level was measured in all babies who appeared "jittery." If hypocalcemia (plasma calcium <7.0 mg/100 ml) was found, calcium gluconate solution was given orally or by intravenous infusion.

Infection and Antibiotics—Increasing attention was paid over the years to the early detection of infection and greater numbers of blood cultures and lumbar punctures were performed. In 1966 the antibiotics most commonly used to treat serious infections were ampicillin and cloxacillin; subsequently, kanamycin and cloxacillin were employed. Prophylactic antibiotics were given to infants when the fetal membranes had been ruptured for more than 24 hours until 1968 (usually ampicillin), and to infants being treated by mechanical ventilation until 1970 (usually kanamycin and cloxacillin). These practices were then abandoned.

Problems of Hemostasis—One milligram of phytonadione (vitamin K,) was given intramuscularly to all infants who appeared "jittery." If hypocalcemia (plasma calcium <7.0 mg/100 ml) was found, calcium gluconate solution was given orally or by intravenous infusion.

Parents—Parents have always been allowed unrestricted visiting but until 1968 they were only rarely allowed into the intensive care area although they could see their children through a glass partition. Since that time we have encouraged them to enter the intensive care area and to handle their infants, even if they were being cared for in incubators.

Follow-up
Infancy (Less Than 3 Years of Age)—After leaving the hospital, the children were seen regularly at a special clinic in the children's outpatient department by one of us (A.L.S.) who had not been
involved in their inpatient care. At each visit they were weighed, measured, and examined clinically and their development was assessed according to Knobloch, Pasamanick, and Sherard's Developmental Screening Inventory\textsuperscript{16} from which a Developmental Quotient (DQ) was calculated. Intervals between clinic visits were dictated by the clinical state of the child, and the competence and confidence of the parents, but never exceeded three months during the first year of life. If growth and development were considered to be normal at the age of 18 months, the interval between assessments was increased to six months. Development was then assessed according to Sheridan's chart.\textsuperscript{17}

\textit{The Preschool Period (3 and 4 Years of Age)—} During the fourth year of life, the first psychological assessment was made, usually in the children's outpatient department by a clinical psychologist who knew nothing of the child's perinatal history, except the period of gestation and the birthweight. Birth rank and parental occupation were also made available to the psychologist. Assessment was usually made with the Revised Stanford Binet (form LM) Intelligence Scale.\textsuperscript{18} The Merrill-Palmer Scale\textsuperscript{19} was also used for children who spoke no English or occasionally for very shy children.

\textit{Older Children (More Than 4 Years of Age)—} Following the first psychological assessment, the children were contacted annually, and the majority attended the outpatient department. At these visits they were measured, examined clinically, and their progress both at home and at school was discussed with the parents. A few children were retested using the Weschler Preschool and Primary Scale of Intelligence\textsuperscript{20} after school entry, particularly if they had been unable to speak English at their first assessment.

\textit{Special Assessments—} Throughout the period of the study any child who was thought to be abnormal in any way was referred for investigation to colleagues with a special interest in the particular abnormality. Investigations carried out included hearing assessments, ophthalmic examinations, and refraction. Children thought to have cerebral palsy or an abnormality of mental development were assessed by a consultant in mental and physical handicap and a child psychiatrist.

\textit{Children Living Abroad—} Reports from parents and local medical attendants were obtained annually. In some cases methods of assessment differed from our own and there were insufficient data to derive developmental or intelligence quotients. These results are reported separately.

\textit{Controls and Parents—} An attempt to collect a control population was abandoned because satisfactory matching for important factors such as ethnic group, social class, maternal age, and parity proved impossible in our hospital which carries out less than 2,000 deliveries per year. In any case, at this stage of the study we can only hope to rule out with certainty handicaps sufficiently severe to interfere with normal function in society. This degree of handicap does not require a control group to establish abnormality.

The intelligence of one parent of each child was tested using the Weschler Adult Intelligence Scale.\textsuperscript{21} The assessment was carried out on the same occasion as the child's first psychological assessment, by a separate psychologist. Except in cases where only one parent spoke English, the parents themselves decided which one was to be tested.

\textbf{RESULTS}

The results are summarized here. Further details are available in the Appendix.\textsuperscript{4}

\textit{The Perinatal and Neonatal Periods—} Sixty of the total of 197 deliveries during the five-year period were to primagravidae, 108 mothers had had previous live or stillborn infants, and 29 had previous abortions only. Abnormalities of pregnancy included threatened abortion or antepartum hemorrhage (64 cases) and pre-eclamptic toxemia (13 cases). Shirodkar sutures had been inserted during 15 pregnancies. Details of the social and obstetric histories of the mothers, and the gestation, birthweight, and sex of the whole population of infants are given in Appendix Table I.

\textit{Survival Rate and Prenatal or Perinatal Events—} Eighty-eight infants died in the first 28 days of life. A further 11 infants died subsequently aged 29 days to 25 months (median, 3 months), leaving 98 children who have survived for longer than 2\<sup>3</sup> years. Tables I and II summarize figures for neonatal (> 28 days) survival rate by birthweight and gestational age. Means and medians for these data, together with particulars of the infants dying later, are given in Appendix Table II. The relation of single or multiple pregnancy, other prenatal factors, and the method of delivery to survival rate are shown in Appendix Table III. The survival rate appeared to be highest among

\textsuperscript{4}See NAPS document 02453 for eight pages of supplementary material. Order from ASIS/NAPS c/o Microfiche Publications, 440 Park Avenue South, New York, N.Y. 10016. Photocopies are $5.00. Microfiche are $1.50 (payable in advance to Microfiche Publications). Outside of the United States and Canada add postage (photocopy, $2.00) microfiche, $0.50).
infants born by cesarean section (69%), followed by forceps-assisted vertex delivery (65%), vertex delivery without forceps (53%), and breech delivery (47%). These differences were not, however, statistically significant.

There were considerable variations in neonatal survival rate from year to year. For example, although the survival rate during the five-year period for infants weighing 1,001 to 1,500 gm was 69%, the range in individual years was from 48% to 85%. No differences were apparent in the survival rates of inborn and outborn infants in the years 1966 to 1970. The neonatal survival rate for infants born in UCH is probably increasing (Appendix Table IV) and in the most recent five-year period, 1968 to 1972, 75% of infants weighing 1,001 to 1,500 gm have survived. Appendix Table IV shows perinatal mortality rates for infants born in UCH and neonatal survival rates both for inborn infants and for those admitted from elsewhere in each of the five study years.

The overall incidence of major birth defects, defined as structural or biochemical abnormalities interfering with normal function, was 6%; that of minor defects, namely structural abnormalities which did not interfere with normal function, was 8%. Details are given in Appendix Table V and are related to survival rate.

The relationship between the sex of the infant and intrapartum or postnatal events to survival rate is shown in Appendix Table VI. Although the survival rate in females (60%) was higher than in males (50%) this difference was not statistically significant ($\chi^2 = 1.79, P<0.2$). The survival rate of the infants who weighed less than the 10th percentile for gestation was higher than for those whose weight lay on or above the 10th percentile ($\chi^2 = 5.65, P<0.02$).

Seventy-nine of the 197 infants were intubated at birth. A total of 74 infants were breathing spontaneously and adequately within five minutes of delivery; 15 between five and nine minutes; and 29 at ten minutes or later. Spontaneous breathing was not established in 27 infants who died. Although there was no significant difference between the mean rectal temperature on admission to the unit of survivors (35.3 ± SE 0.1 C) and of infants who died (34.4 ± 0.2 C), a temperature below 35 C was associated with a reduced survival rate ($\chi^2 = 10.08, P<0.005$).

The presence of a severe intrapartum or postpartum metabolic acidosis, presumably due to hypoxia, shortly after birth; a low body temperature on arrival in the unit; and hyaline membrane disease sufficiently severe to necessitate mechanical ventilation. Apart from the deleterious effects of decreasing birthweight and gestational age, no other adverse influences affecting survival could be identified.

Autopsy

By far the most common diagnoses at autopsy were hyaline membrane disease and intraventricular hemorrhage, either or both of these findings being regarded as the main cause of death in 56 (58%) of the infants. The main findings and the clinically diagnosed causes of death in the 18 infants weighing less than 800 gm who were not autopsied are given in Appendix Table VII.

Follow-up

Three of the 98 long-term survivors who had returned with their parents to Nigeria, Ghana, and Germany could not be traced. Data were available for the remaining 95 children including detailed assessments of 85 children who were attending our own clinic and 4 who have been assessed by colleagues on our behalf. During the first four years the child's age was regarded as his
chronological age less the weeks that he had been born before term. For infants aged 5 years or more this correction was no longer considered to be necessary.

The term *handicap* as used below is defined as an abnormality sufficiently severe to interfere with present or future normal function in society.

**Growth**—Measurement of height (89 children) and weight (95 children) between the ages of 2 and 6 years (mean, 4 years 9 months) have been compared with Tanner and Whitehouse’s standards for London children. No corrections were made for ethnic group or for parental height. The height of 13 (15%) of the children lay on or above the 75th percentile, 37 (42%) were between the 25th and 74th percentiles, 21 (23%) between the 10th and 24th percentiles, and 18 (20%) below the 10th percentile. For weight the distribution was similar: 9 (11%) were on or above the 75th percentile, 28 (33%) lay between the 25th and 74th percentiles, 26 (31%) were between the 10th and 24th percentiles, and 22 (25%) were below the 10th percentile. Taking only the 20 infants who were light-for-dates at birth (< 10th percentile), ten remained below the 10th percentile for height or weight or both.

**Intelligence Quotients**—The distribution of the IQs of the 65 older children obtained at a mean age of 3 years 6 months (range, 2 years 11 months to 5 years 9 months), is shown in Figure 1. The IQs of one parent of 59 of the children are also shown for comparison. The distribution of values obtained in the children was no different from that of their parents. Sixty (92%) of the children had an IQ of 80 or above.

The IQs of three handicapped children fell within the very inferior (IQ < 68) range (Fig. 1), including a girl who had been transferred from a normal primary school to a special school, and two boys one of whom attended a normal school and the other a special school for the severely mentally handicapped. The mental development of two other handicapped children with IQs in the inferior range (68 to 83) was also regarded as potentially abnormal. One child, a girl, had a specific language-learning difficulty. She was also partially deaf (see below), but this was thought to be insufficient to account for her problems and a diagnosis of minimal cerebral dysfunction was made. The other child, a boy with cerebral palsy and an IQ at the lower end of the inferior range, may need special educational provision for mental as well as physical handicap.

**Development of Younger Children**—Twenty-four children born in 1970 were too young for IQ testing. The results of the last DQ measurements performed using the Knobloch et al. Screening Inventory, at a mean age of 16 months (range, 12 to 18 months) gave 4 children a DQ of 80 to 89, 8 a DQ of 90 to 99, and 12 a DQ of 100 or more. Sheridan’s chart, which was used for subsequent assessments does not allow the derivation of a DQ. However, apart from two handicapped children with spastic diplegia (see below) whose development was satisfactory in all other than motor areas, the children were continuing to develop normally at a mean age of 3 years 3 months (range, 2 years 10 months to 3 years 7 months).

**Cerebral Palsy.** A total of four handicapped children had cerebral palsy, including three girls with spastic diplegia. The eldest child was fully mobile and attended a normal primary school. The fourth child, a boy, had a right hemiparesis, and his IQ was at the lower end of the inferior range.

**Convulsions.** Four children had had one febrile convulsion each. There were no children with epilepsy.

**Hearing:** One handicapped girl had a hearing loss of 40 dB, due to chronic inflammatory disease of the middle ear.

**Vision:** One handicapped girl was partially sighted as a result of congenital cataracts. The etiology of the cataracts is unknown and virus studies were negative. Her intelligence was within the normal range. Another girl had Duane syndrome, with a total left VI nerve palsy. The results of surgery were cosmetically excellent and handicap consequent on visual abnormality is considered to be unlikely. Nine children including two siblings and another child with affected siblings had refractive errors. Eight of the nine presented with squints. None were handicapped by their refractive errors.

**Incompletely Assessed Children Living Abroad:** Six children, including three siblings, were living abroad and have been incompletely assessed. At ages between 2 years 10 months and 6 years 11 months (mean, 5 years 4 months) they were all regarded as normal children by their parents and local medical attendants.

**Summary of Physical and Mental State of Surviving Children**—Table III summarizes the physical and mental state of the total population of 95 children.

**Cause of Handicap**—The presence of handicap was very significantly related to the occurrence of presumed severe hypoxia (Table IV) in the perinatal or neonatal period, particularly if accompanied by jaundice. We suspected that severe hypoxia had occurred in two circumstances; firstly when a base excess less than −15 mEq/liter was found in the first sample obtained within two hours of delivery indicating intrapartum or post-
partum hypoxia; and secondly, when an infant became apneic and required endotracheal intubation. Among the 28 infants who fell into one or both of these categories, eight (29%) were found to be handicapped (χ² vs non-"hypoxic" infants = 13.87, P<0.001). Eleven of the 28 "hypoxic" infants were jaundiced, with maximum indirect serum bilirubin levels above 10 mg/100 ml (mean, 14.2 mg/100 ml; range, 11.4 to 18.4 mg/100 ml); of these 11, six (54%) were handicapped (χ² vs "hypoxic" nonjaundiced infants = 4.08, P<0.05).

No other statistically significant adverse relationship with obstetric or perinatal illnesses, either alone or in combination, affecting the incidence of handicap could be identified. There were no handicapped children among the 23 who had run an uncomplicated course, and only one proved to be handicapped among the 44 who had had illnesses or complications such as hyaline membrane disease (18 infants), hypoglycemia (5 infants), jaundice (19 infants), or a delay in regaining the birthweight of more than 21 days (14 infants), but had not suffered from "presumed severe hypoxia." Appendix Table VIII gives details of the nine handicapped children including their perinatal histories. Appendix Tables IX and X show the incidence of handicap following specific perinatal events.

**DISCUSSION**

The program of care for infants of very low birthweight which was employed in our unit when this study began was intended to anticipate and prevent, as well as treat, any abnormality which might be lethal or result in damage to the central nervous system. This program, which has continued to develop subsequently, was particularly concerned with the prevention of hypoxia both before and after delivery. For example, facilities were provided for prompt resuscitation at birth, the monitoring of breathing, rapid analysis of arterial oxygen tension, and mechanical ventilation. The nursing staff was trained in resuscitation using, if necessary, endotracheal intubation, so that apneic spells could rapidly be overcome, even if no member of the medical staff was present. The infants were hydrated and fed from the first day of life, and biochemical abnormalities such as hypoglycemia and hyperbilirubinemia were avoided whenever possible.

**Survival Rate**

The survival rate of the infants increased after the introduction of these methods of care. For example, only 45% to 50% of those weighing 1,001 to 1,500 gm survived in the 1950s and early 1960s, whereas the survival rate for inborn and outborn infants averaged 69% and 70%, respectively, during 1966 to 1970, the five-year period under review (Table I and Appendix Table IV). During this period 50% of those infants who were born at gestational ages of 28 to 29 weeks survived (Table II). Among inborn infants the survival rate has probably continued to increase (Appendix Table IV). Since our hospital is a referral center for high-risk pregnancies, as well as for infants requiring intensive care, and since our survival figures are well above the national average, we infer that the use of intensive care methods is largely responsible for our improved results.

**Follow-up**

Most of the earlier follow-up studies of infants of very low birthweight concerned those who had survived from a time when little was known of their normal or abnormal physiology and facilities for intensive care were not available. Certain features of the management of the infants in the perinatal period may at that time have been actively harmful: for example, the limitation of inspired oxygen concentration to below 40% under all circumstances in order to reduce the incidence of retrolental fibroplasia, and the practice of starving the infants in the first days or weeks of life, which was probably responsible for promoting metabolic abnormalities such as hypoglycemia and hyperbilirubinemia, as well as depriving the developing brain of an adequate supply of calories. These early studies gave a uniformly poor prognosis for survivors who had weighed less than 1,500 gm at birth, with handicap rates ranging from 33% to 60%.

The present study has confirmed our preliminary report that the prognosis for infants of very low birthweight can now be very much better. Only nine (9.5%) of the 95 children have handicaps which will prevent them from functioning normally in society (Table III), and the distribution of the IQs of the older children was no different from that of their parents (Fig. 1). Among these nine, only five or possibly six had abnormalities of mental or physical development which required, or may require, special educational facilities. All the children were beyond the age when Drillien had identified major handicap in her 1958 study and 45 of them were attending school. It is, therefore, most unlikely that any serious handicaps remained undiscovered, although we cannot, of course, be sure that learning difficulties or minor abnormalities of, for example, coordination, may not be detected later. We propose to keep the children under surveillance and test them accordingly.
TABLE III
SUMMARY OF NUMBERS OF CHILDREN WITH AND WITHOUT HANDICAP AT A MEAN AGE OF 5 YEARS 2 MONTHS (RANGE, 2 YEARS 10 MONTHS TO 7 YEARS 10 MONTHS)

<table>
<thead>
<tr>
<th>Total No. of children</th>
<th>95</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children without handicap</td>
<td>86 (90.5%)</td>
</tr>
<tr>
<td>Children with handicap</td>
<td></td>
</tr>
<tr>
<td>Physical handicap only</td>
<td></td>
</tr>
<tr>
<td>Partially sighted</td>
<td>1</td>
</tr>
<tr>
<td>Spastic diplegia</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>Mental, with or without physical handicap</td>
<td></td>
</tr>
<tr>
<td>IQ &lt;68</td>
<td>3</td>
</tr>
<tr>
<td>Minimal cerebral dysfunction, IQ 79</td>
<td>1</td>
</tr>
<tr>
<td>Hemiparesis, IQ 70</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>5 (5.3%)</td>
</tr>
</tbody>
</table>

Cause of Handicap
In spite of our efforts to prevent it, by far the most important immediate cause of death was hypoxia, due either to intrapartum or postpartum asphyxia, or hyaline membrane disease requiring mechanical ventilation (Appendix Table VII). Coexisting intraventricular hemorrhage, itself probably caused by hypoxia, was frequently found at autopsy. The only other important factors which influenced survival rate were birthweight and gestational age. Not surprisingly, the highest mortality was among the smallest infants (Table I), and only 23% of those weighing 501 to 1,000 gm survived. Birth defects were rarely a cause of death (Appendix Table V), serious infection was uncommon (Appendix Table VII), and no relation could be found between specific abnormalities of pregnancy and survival rate (Appendix Table III).

Cause of Death
The number of handicapped children was small; nevertheless, a clear relation between the presence of handicap and the occurrence of neonatal illnesses, particularly those presumed to have caused severe hypoxia, was established (Table IV and Appendix Table X). It was striking that there were no handicapped children among the 23 who were free of serious neonatal difficulties and only one of the 44 who suffered from a variety of problems such as hyaline membrane disease, preterm apnea, hypoglycemia, and jaundice but who had apparently not had any severe hypoxic episodes proved to be handicapped. These findings applied equally to infants who were light-for-dates and to those who were solely preterm. By contrast, eight out of the nine handicapped children had probably suffered severe hypoxia around the time of birth (as judged by the discovery of a large metabolic acidosis soon after delivery), or subsequently (as indicated by the development of apnea necessitating endotracheal intubation). The incidence of handicap in infants with either or both of these findings was 29% (Table IV). Hypoxia, therefore, seemed not only to be the most important cause of death, but also the most important cause of handicap. Seven of the nine handicapped children were jaundiced and the incidence of handicap among the 11 children in whom presumed hypoxia and indirect serum bilirubin levels between 10.8 and 18.4 mg/100 ml both occurred was 54% (Table IV). Serum bilirubin levels as high as this without hypoxia appeared innocuous. The reason for the apparent potentiation of the adverse effect of hypoxia by jaundice may have been, in some cases at least,
that low pH was responsible for detaching bilirubin from albumin so that it could penetrate into the brain.31

No other significant associations between handicap and social or obstetric factors, or perinatal events, could be discovered. Since starvation in the neonatal period has been implicated in the causation of handicap or reduced IQ in low-birthweight infants,27,32 particular attention was paid to the possibility that poor weight gain might predispose to handicap. Although five of the nine handicapped children were still below their birthweight on the 21st day (Appendix Table VIII), so too were 20 of the nonhandicapped children ($X^2 = 2.87, \text{N.S.}$), even though we tried to increase their caloric intake as rapidly as possible. Four of the five also suffered from hypoxia and jaundice. We doubt, therefore, whether the degree of undernutrition experienced by the infants in the present study (who were fed from arrival in the unit) was sufficient to cause handicap. While it is highly probable that severe starvation can damage the developing brain,33 another explanation for the association of delayed weight gain and subsequent handicap and low IQ which seems at least as probable from our data is that both are caused by severe illness, particularly if accompanied by hypoxia and jaundice.

**Implications and Conclusions**

Studies from other centers34,35 confirm our findings that the application of intensive care methods to infants of very low birthweight is associated both with an increase in survival rate and a reduction in the proportion who will be handicapped. We therefore conclude that much of the high mortality and morbidity found by previous workers was caused by preventable perinatal events, and we also conclude that the intensive care of these infants is worthwhile for social and economic as well as purely humanitarian reasons. It follows that facilities for carrying it out should be provided on a wide scale. Because less than 2% of live-born infants in this country weigh 1,500 gm or less at birth and because they are so susceptible to hazards which may kill or handicap them, we believe that they should whenever possible be delivered in major centers which are properly equipped to provide optimal care both before and after birth. Failing this, they should be transferred immediately after delivery to neonatal intensive care units. With improvements in the methods for the transfer of small or sick infants, the risks of transfer will often be less than the dangers of remaining in a hospital with inadequate facilities.

Many infants of very low birthweight still die and our handicap rate of 9.5% remains unacceptably high. Since this study indicates that intrapartum or postpartum hypoxia is largely responsible for death and handicap in these infants, advances in methods which combat hypoxia, or the illnesses which cause it, are likely to produce the greatest further improvement in prognosis. For example, the increasing use of intrapartum monitoring will ensure that more infants are born in good condition. Also, since the survival rate in the present investigation appeared to be highest in infants delivered by cesarean section and lowest among breech deliveries (Appendix Table III), who are likely to have suffered the worst hypoxia, it seems that a low threshold for cesarean section can safely be encouraged when a very small fetus is at high risk in utero.

During recent years substantial advances have

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**TABLE IV**

<table>
<thead>
<tr>
<th>Infants</th>
<th>Total No.</th>
<th>No. of Handicapped</th>
<th>Handicapped (% of Total)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without &quot;presumed severe hypoxia&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without jaundice</td>
<td>48</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>With jaundice</td>
<td>10</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>67</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>With &quot;presumed severe hypoxia&quot;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without jaundice</td>
<td>17</td>
<td>2</td>
<td>18</td>
</tr>
<tr>
<td>With jaundice</td>
<td>11</td>
<td>6</td>
<td>54</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>8</td>
<td>29</td>
</tr>
</tbody>
</table>

*Hypoxia: base excess—15 mEq/liter or less in the first sample obtained within two hours of birth or apnea at any age (other than immediately after delivery) necessitating endotracheal intubation; jaundice: maximum serum bilirubin 10 mg/100 ml.*
been made in the management of the most important lethal postnatal cause of hypoxia, hyaline membrane disease. The prenatal detection of infants at risk for the illness allows some pregnant women to be prolonged until the lungs are sufficiently mature to avoid the likelihood of developing it, and the antenatal treatment of infants with immature lungs may soon become feasible. The introduction of methods for maintaining alveolar inflation during spontaneous breathing and of better methods for mechanical ventilation have much improved the chances for infants with the established illness in our unit in the years since the study period ended. Because of the association of jaundice together with hypoxic episodes and subsequent handicap, we have intensified our efforts to prevent and treat jaundice in infants who are either thought to have suffered hypoxia or who are considered to be at risk for it.

Other changes in management which have taken place and which may be expected to cause a further improvement in prognosis include the introduction of parenteral nutrition, which has proved very useful in the management of the smallest infants, and the routine measurement of coagulation status, which allows infants at risk for bleeding to be treated prophylactically.

REFERENCES


ACKNOWLEDGMENT

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We thank Professor L. B. Strang for his constant help and encouragement throughout the study, the medical and nursing staff of the neonatal unit for their devoted care of the infants, and the many doctors, nurses, and psychologists both at University College Hospital and at other centers at home and abroad who have helped with the follow-up study. In particular, we should like to thank Miss Grace Rawlings, who supervised the psychological aspects of the investigation, and Dr. Cecil Drillien for many stimulating discussions.

Who Invented the Ice Cream Sundae?

The ice cream sundae emerged in the late 1890s and became extremely popular around the turn of the century. This popularity was substantially aided by laws prohibiting the sale of sodas on Sunday, and for this reason the concoction was first known as the “Sunday” or the “Soda-less Soda.”

The more elegant -ae ending probably came about when those who orated from the pulpit on the sinful soda went to work on the sacrilegious use of the name of the Sabbath for its stand-in.

As for the specific birthplace of the dish, two possibilities emerge as the most likely among many contenders. Neither place can offer conclusive dates, so one can pick between “Heavenston” (favored by the National Dairy Council, among others) and Two Rivers (championed by such diverse sources as the old Ice Cream Review and H. L. Mencken in his American Language).

The first claim goes back to the 1890s in Evanston, Illinois (then widely known as “Chicago’s Heaven” or “Heavenston”), where civic piety had reached such a state that it became the first “Sunday Soda Menace.” This prompted confectioners to create Sundays so that they could do business on the Sabbath. Ironically the soda was later given a strong boost from this community when the Evanston-based Women’s Christian Temperance Union (WCTU) championed it as a pleasant alternative to alcoholic drinks.

The Two Rivers, Wisconsin, claim goes back to the same era and, so the story goes, was created when a youth named George Hallauer went into Ed Berner’s soda fountain for a dish of ice cream. As the ice cream was being scooped, the daring Hallauer spied a bottle of chocolate syrup norm—over his ice cream. Berner sampled the concoction and liked it enough to begin featuring “ice cream with syrup” in his shop for the same price as a dish of ice cream. The name sundae was given to the dish when George Giffy, an ice cream parlor proprietor in nearby Manitowoc, was forced by customer demand to serve the popular Berner concoction. Giffy was convinced that the nickel dish would put him out of business and at first served it only as a Sunday loss leader. In Manitowoc it soon became known as “the Sunday.”

Giffy soon found that he was making money on the dish and began advertising his “Ice Cream Sundae,” with the spelling changed so that it would lose its Sunday-only association.

PAUL DICKSON

The Great American Ice Cream Book

New York: Atheneum, 1973

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Ann L. Stewart and E. O. R. Reynolds
Pediatrics 1974;54;724

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