1 Milestones in neonatology

The care of newborn infants has evolved over the last century from simple and empirical care to modern, evidence-based, high-tech medicine. Neonatal mortality has correspondingly declined dramatically from 40/1000 livebirths in 1900 to 4/1000 in 2003 in the US and UK. Improved obstetric care and maternal health and nutrition have also contributed. It was only in the 1950s that medical care of healthy and sick newborn infants was transferred from obstetricians to pediatricians. The specialty of neonatology developed only in the 1960s, and the first certifying examination for physicians in the US was held in 1975.

Incubators/thermal regulation

- 1890s: Tarnier in France showed that a warm, controlled environment reduced mortality of infants <2 kg from 66% to 38% (Fig. 1.1).
- 1893: Budin, Tarnier's student, established the first unit for premature babies in Paris, emphasizing thermal regulation and breast-feeding.
- Early 1900s: premature babies in incubators were exhibited in fairs around Europe and the US (Fig. 1.2).
- 1950s: Silverman in the US conducted elegant randomized controlled trials to confirm the beneficial effects of thermal control (including humidity) on mortality.

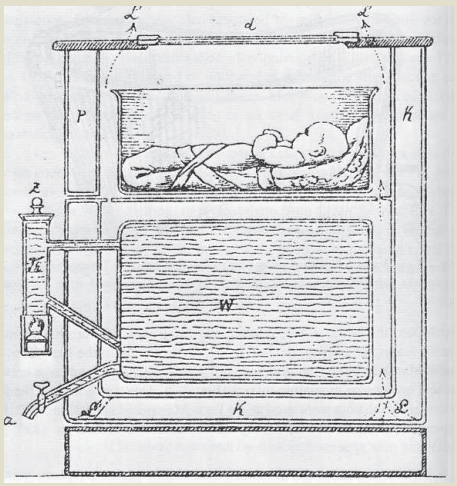

Fig. 1.1 The Tarnier incubator. The water was heated by the oil flame. The baby was kept warm by the heated air circulating around the incubator.

Fig. 1.2 Incubators with premature babies at the Pan-American Exposition, Buffalo, New York in 1901. (Source: Silverman WA. Incubator-baby side shows. *Pediatrics* 1979; **64**:127. Courtesy of the American Academy of Pediatrics.)

Nutrition

- 1880s: Tarnier and Budin recommend early feeding and intragastric 'gavage' feeding via a rubber tube.
- 1907: Rotch in US introduces infant formula. Breast-feeding declines as some believed formula was superior.
- 1940s: Gavage feeding via a nasogastric tube used in neonatal units.
- 1940s: Feeding of preterm infants delayed up to 4 days to avoid aspiration. Adverse effects (hypoglycemia, increased bilirubin and impaired development) recognized only in the 1960s, and early feeding reintroduced.
- 1960s: TPN (total parenteral nutrition) by central venous catheter introduced centrally, then via peripheral veins.
- 1960s: Infant formula associated with neonatal tetany from hypocalcemia and hemolysis from vitamin E deficiency.
- 1980s: Development of special formulas for very low birthweight infants.
- 1980s: Resurgence of use of breast milk. Human milk fortifiers developed for preterm infants.
- 2000s: Addition of long-chain polyunsaturated fatty acids (LCPUFA) to formula.

Antibiotics

Before antibiotics, mortality from neonatal sepsis was almost 100%, but it declined markedly when penicillin was introduced in 1944. The organisms causing sepsis have changed (Fig. 1.3).

Fig. 1.3 Change with time of main organisms causing neonatal infection.

Rhesus hemolytic disease

Kernicterus, from bilirubin deposition in the brain from rhesus disease, was first described in 1938. Exchange transfusions became a common procedure in neonatal units and saved an estimated 8000 lives/year in the US alone. Rhesus disease is now almost completely prevented by prophylaxis.

- 1925: Hart describes first exchange transfusion – blood in via saphenous vein, out from anterior fontanel.
- 1940: Landsteiner discovers rhesus factor.
- 1945: Coomb develops Coomb's test (direct antiglobulin test, DAT) to detect rhesus agglutinins.
- 1947: Diamond describes exchange transfusion via umbilical vein with rubber catheter.
- 1963: Liley introduces intrauterine transfusion.
- 1964: Freda and Clarke develop prophylaxis with anti-D immunoglobulin.

Respiratory distress syndrome (RDS)

Oxygen therapy, monitoring and respiratory support

Whereas about 25 000 infants died every year in the US from RDS in the early 1950s, by 2003 there were fewer than 500 such deaths. This has resulted from:

- understanding the pathogenesis of RDS, which enabled development of surfactant replacement therapy
- antenatal corticosteroids to induce surfactant and lung maturation
- developments in respiratory support:
  - oxygen therapy
  - mechanical ventilators, first shown to improve survival by Swyer in Toronto and Reynolds in London (1965); continuous positive airway pressure (CPAP) introduced by Gregory
- ability to closely monitor vital signs and blood gases
  - cardiorespiratory monitors for neonates
  - measurement of blood gases on small blood samples
  - umbilical/peripheral artery catheters
  - transcutaneous arterial O_2 and CO_2 monitors
  - non-invasive oxygen saturation monitors.

History of respiratory distress syndrome (surfactant deficiency)

- 1955: Pattle describes properties of surfactant.
- 1956: Clements isolates surfactant.
- 1959: Avery and Mead demonstrate lack of surfactant in preterm lungs.
- 1972: Liggins and Howie – prenatal corticosteroids induce lung maturity.
- 1980: Fujiwara – first surfactant replacement therapy.
- 1985: Multicenter clinical trials of natural and artificial surfactant replacement therapy.
- 1989: Surfactant therapy approved.

Key point

For the last 50 years RDS has been the major focus of research in neonatology. Understanding its pathophysiology and the biochemistry of surfactant has been the key to developing surfactant replacement therapy and designing appropriate respiratory support, which have dramatically decreased mortality.

Development of neonatal intensive care

- 1922: First neonatal unit in US in Chicago by Hess; in UK by Crosse in Birmingham in 1945.
- 1960s and 1970s: Development of regional neonatal intensive care units with dedicated staff, introduction of CPAP and mechanical ventilation.
- 1970s: Ultrasound to identify intraventricular hemorrhage.
- 1970s: Ability to safely perform surgery in tiny infants.
- 1980s: Development of multicenter clinical trials, national and international.
- 1980s: ECMO (extracorporeal membrane oxygenation).
- 1990s: NO (nitric oxide) therapy for persistent pulmonary hypertension of the newborn.

Challenges for the future

- Reduce prematurity, hypoxic–ischemic brain injury, neonatal infection, congenital abnormalities.
- Avoid complications of preterm infants: brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia (chronic lung disease), retinopathy of prematurity.
- Practice evidence-based medicine.
- Reduce iatrogenic disease, e.g. medication errors.
- Develop better non-invasive monitoring.
- Enhance nursery environment.
- Confront ethical dilemmas at the limit of viability.
- Improve and extend care at home of technology-dependent infants.