



# 1 Milestones in neonatology

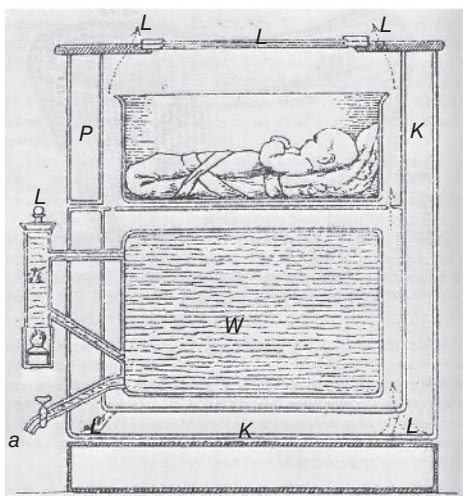
The care of newborn infants has evolved over the last century from simple and empirical care to modern, evidence-based, high-tech medicine. Neonatal mortality has correspondingly declined dramatically from 40/1000 live births in 1900 to <4/1000 in the US and UK. Improved obstetric care and maternal health 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.

## Thermal regulation

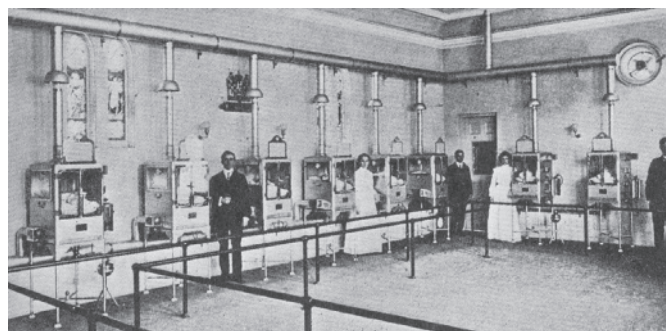
- 1890s: Tarnier in France showed that a warm, controlled environment reduced mortality of infants <2 kg from 66% to 38% (Figure 1.1).
- 1893: Budin, Tarnier's student, established the first unit for premature babies in Paris, emphasizing thermal regulation and breast-feeding.
- Early 1900s: Premature babies in incubators were exhibited in fairs around Europe and the US (Figure 1.2).
- 1950s: Silverman in the US conducted elegant randomized controlled trials to confirm the beneficial effects of thermal control (including humidity) on mortality.
- 2000s: Heat loss at delivery of extremely preterm babies minimized by plastic wrapping.

## Nutrition

- 1880s: Tarnier and Budin recommend early feeding and intragastric "gavage" feeding via a rubber tube inserted through the mouth.
- 1907: Rotch in US introduces infant formula. Breast-feeding declines as some believed formula was superior.



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



**Figure 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.

- 1940s: Gavage feeding via a nasogastric tube used in neonatal units.
- 1940s: Feeding of preterm infants delayed up to four days to avoid aspiration. Adverse effects (hypoglycemia, increased bilirubin and impaired development) recognized only in the 1960s, and early feeding reintroduced.
- 1960s: Parenteral nutrition (PN) introduced by central venous catheter, then via peripherally inserted central catheters (PICC) lines.
- 1960s: Infant formula associated with neonatal tetany from hypocalcemia and hemolysis from vitamin E deficiency.
- 1980s: Development of special formulas for very low birth-weight 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.

## Rhesus hemolytic disease

Kernicterus, from bilirubin deposition in the brain in 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.

- 1925: Hart describes first exchange transfusion – blood given via saphenous vein, removed from anterior fontanelle.
- 1940: Landsteiner discovers rhesus factor.
- 1945: Coombs develops Coombs 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.
- 1968: Rho(D) immune globulin prophylaxis introduced. Rhesus disease now almost completely prevented in high income countries.

## 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 (Figure 1.3).

## Respiratory distress syndrome (RDS)

### 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 show that prenatal corticosteroids to the mother induce fetal lung maturity.
- 1980: Fujiwara – first surfactant replacement therapy.
- 1985: Multicenter clinical trials of natural and artificial surfactant replacement therapy.
- 1989: Surfactant therapy approved.

### Oxygen therapy, monitoring, and respiratory support

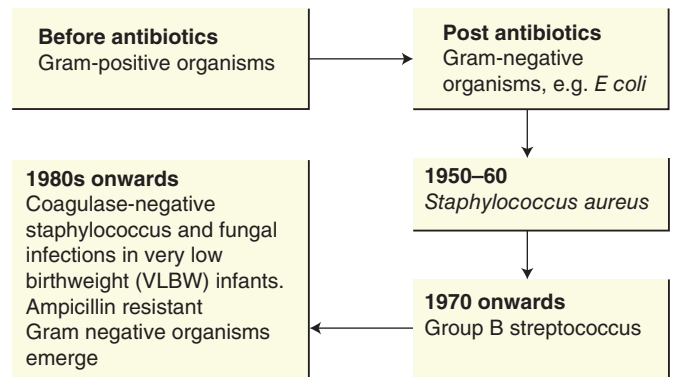
Whereas about 25 000 infants died every year in the US from respiratory distress syndrome (RDS) in the early 1950s, by 2003 there were fewer than 500 such deaths.

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.
  - continuous positive airway pressure (CPAP), introduced by Gregory.
  - mechanical ventilators, first shown to improve survival by Swyer in Toronto and Reynolds in London (1965).
- 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
  - non-invasive oxygen saturation monitors.
- 2010s: increasing use of non-invasive respiratory support to avoid or reduce mechanical ventilation.

### Key point

Since the 1950s RDS has been a major focus of research in neonatology. Understanding its pathophysiology and the biochemistry of surfactant has been the key to developing surfactant therapy and respiratory support, which have dramatically improved survival.



**Figure 1.3** Change with time of main organisms causing neonatal infection.

## 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: Extracorporeal membrane oxygenation (ECMO).
- 1990s: Nitric oxide (NO) therapy for persistent pulmonary hypertension of the newborn.
- 2000s: Mild hypothermia shown to reduce morbidity of hypoxic-ischemic encephalopathy.
- 2010s: Non-invasive prenatal testing (NIPT) – free fetal DNA analysis from maternal blood for Trisomy 21 etc.
  - Whole genome sequencing for critically ill newborns

## Challenges for the future

- Reduce prematurity, hypoxic-ischemic brain injury, neonatal infection, congenital abnormalities.
- Prevent complications of prematurity: brain injury, necrotizing enterocolitis, bronchopulmonary dysplasia, retinopathy of prematurity.
- Practice evidence-based medicine.
- Improve patient safety – reduce medication errors etc.
- Develop better non-invasive monitoring.
- Enhance nursery environment and parental satisfaction.
- Confront ethical dilemmas at the limit of viability and withdrawal of life support.
- Improve/extend care at home of technology-dependent infants.
- Develop personalized medicine incorporating modern genetics.
- Global reduction of neonatal mortality (2.5 million in 2018).