

<p style="text-align: center;">CHAPTER 2: EXTREME PREMATURITY: CHANGES IN MEDICAL APPROACHES TO SURVIVAL</p>

2.0 Introduction

Infants born at the edge of viability are at a profound disadvantage. They are suddenly taken from a warm uterine environment, and are required to adapt to life within the confines of an incubator in the NICU. Successful transition to extrauterine life requires changes from the placental to pulmonary circulation, and changes from the fetal to the neonatal circulation. For the extremely premature infant this transition occurs at a time when there may not be sufficient pulmonary circulation for gas exchange to occur. Enforced extrauterine adaptation and existence prior to the maturation of the major organ systems is generally the cause of the major problems of extreme prematurity. This chapter outlines growth and development of the developing fetus and the problems that are likely to be encountered by infants of 24 weeks gestation and less, and. The chapter gives a brief history of neonatal care, in order to show how caring for extremely premature infants has been a series of progressions over time. Results of outcome studies, limited as they are related to infants of 24 weeks gestation and less, are reviewed, allowing for the appreciation of outcomes for extremely premature infants.

2.1 The history of neonatal care

Infants have been born prematurely since the beginning of recorded time, and their prognosis has been discussed in early texts. Sages of the Babylonian Talmud (approximately 200 C.E), described the appearance of “*the prematurely born infant as exhibiting an absence of hair and nails...it was believed that babies born in the eighth month of gestation were nonviable, whereas those born in the seventh of ninth months of gestation were viable.*” (cited in Dweck 1991, p. 426). Hippocrates around 406 BC believed that it would be impossible to break through the 28-week gestation barrier (Humes 2000, p. 119). Shakespeare made the character of King Richard III a premature

infant, even though the original Richard Plantagenet (The Richard III Foundation 2003) was not born prematurely.

Deform'd, unfinish'd, sent before my time

Into this breathing world, scarce half made up,

(Shakespeare 1591 The tragedy of King Richard III, act 1, sc.1, l. 28)

The interest in the premature infant originated in France in the 1870s. France had lost many citizens as casualties of the Franco-Prussian war during 1870-1871, and there was also a decline in the national birth rate (Baker 1991, p. 654). Interest in the premature infant was not instituted out of sentiment, but to ensure rapid growth of the population.

Before the 19th century premature infants were not considered a distinct category of infants, therefore they were not a problem requiring a solution. In the 19th century physicians tended to categorise premature and weak infants together with feeble and debilitated infants. At this time premature infants were considered to be immature in terms of their size, rather than gestation. During the latter half of the 19th century medical professionals started to show an interest in premature infants (Baker 1996, p. 13).

Pierre Budin is considered to be the father of neonatology. In 1888 he identified three basic problems of management for premature infants including “their temperature and their chilling, their feeding, and the disease to which they are prone” (Cited in Silverman 1979, p. 128). Budin's revolutionary ideas included grouping together healthy premature infants, and isolating sick and suspect infants. This is the basis of the modern neonatal intensive care nursery.

The impetus for neonatal intensive care (NIC) in the USA came when President John F. Kennedy's son Patrick was born on August 7th 1963, weighing 2100 grams at 34 weeks gestation (Richardson, 2001, p. 1501), and died from respiratory failure after only 39 hours of life. Patrick was born six weeks prematurely, and by today's standard an infant of this gestation would cause little concern. However, in 1963 scientists had not

discovered that surfactant was the substance missing from a premature infants lungs. Although the baby's death was a national tragedy, it also set off a chain of events that triggered the rapid rise in neonatal intensive care. Doctors were helpless and unable to save the son of the President of the USA. Massive amounts of money were subsequently diverted into care for the newborn.

Premature infants are even the subject of fiction. Brown (2000) wrote a book called "The hatbox baby", the story of a tiny baby who was born at home unexpectedly and taken by his father to the Century of Progress Exposition at the World's Fair in Chicago. This work of fiction has its origins in the baby incubators sideshows which sprang up at the World Expositions in the USA, and where much of the care of tiny infants was refined before the advent of NICUs. Much of the history of neonatal care has been romanticised, at a time when many infants succumbed from the treatment.

Ethical dilemmas related to the care of extremely premature infants did not arise until the 1960s, because prior to that time there were no options for neonatal intensive care.

Resuscitation was attempted only if the infant was in good condition at birth.

Sophisticated neonatal technology did not exist. An infant, if it was to survive, did so regardless of the care it received. During the 1970s infants weighing less than 1000 grams had a definite chance of survival (Cerase 1988, p. 70), however it was rare for an infant of 24 weeks and less to survive. Kopelman (1978) speaks of the years 1973 and 1974 when he states that in the UK 5.1% of pregnancies resulted in preterm delivery, however they accounted for 85% of early neonatal deaths. Bachrach (1992, p. 977) states "...an 800g baby in 1976 was at the edge of viability in the same way that an infant of 400g is today". The dilemmas associated with microprems have been created from the 1980s. These dilemmas are now more accentuated as technology exists that can save these infants. Questions now centre on whether the infant should be saved and not on can the infant be saved.

2.2 Experimentation in the name of progress

While modern intensive care of the newborn has its origins in the 1960s, historically experiments have been performed on infants, mostly without the consent of the parents, or the informed consent of the parents. The USA was slow to adopt the Nuremberg code of ethics that arose from the Nuremberg experiments in World War Two. According to Rothman (1991) the American research community considered the Nuremberg code “irrelevant to its work”. (p. 31) Doctors believed that they would not act unethically when it came to research subjects. Many infant research subjects came from orphanages because it was a widely held belief at the time that, “...orphans could repay their debt to society through service as research subjects” (Lederer 1995, p. 106).

Orphans

were also used because they were “...cheaper than animals” (Welch, cited in Lederer 1995, p. 69). The discovery of new knowledge was all that mattered to researchers as stated by Berkley (cited in Lederer 1995) “simply a placing of science above morality in the hope that the experimenter might feel the swelling of pride as he realized that he had added another mite of knowledge to scientific research” (p. 71). The overzealous pursuit of knowledge and the total disregard for human life is summed up by Slosson (1895, cited in Lederer 1995) who believed that “a human life is nothing compared to a new fact in science” (p. 45).

Even in modern times the history of neonatal intensive care is one of adopting new therapies before they have been researched (Silverman 1985; Silverman 1998; Lantos & Meadow 2006; Levy 2006). Untried treatments resulted in harm, as many of these therapies damaged the infants. The use of routine oxygen in the care of premature infants resulted in an epidemic of blindness called retrolental fibroplasia (RLF). Terry (1942) first described RLF, and it reached epidemic proportions in the 1940s. Not until the 1950s was its relationship with oxygen suspected and confirmed by Kinsey (1956). Doctors had started to administer oxygen to all premature infants, not just sick ones.

A defensive reaction followed and the therapeutic effects of oxygen were denied for fear it would cause blindness (Drack 1998, p. 1620; Lee 1999, p. 31). Silverman (1985; 1998;

2003) has written extensively about the use of untested therapies on neonates and stated, “...from the belated realization that a seemingly benign intervention like oxygen – a time honoured life-saving drug – could have such unexpected, unrecognized and devastating consequences, we realized that almost everything we were doing to care for premature infants was untested” (Silverman 2003, p. 3). The role of oxygen in the development of RLF is still not fully understood.

In the new millennium there is some evidence that the care of infants 24 weeks gestation and less is experimental. There are few extremely premature infants and evidence is still mounting as to the best way to treat them. Research should adequately test treatments prior to use on human subjects. Technology needs to be fully researched before being implemented into the NICU, however, this does not always occur. Lucey (2004, p. 1819) refers to this as “therapy creep”. One example of the adoption of technology before it has been adequately researched is the use of high frequency jet ventilation (HFJV) to treat respiratory distress syndrome (RDS) in extremely preterm infants. This therapy has made its way into many NICUs and yet the best evidence (Bhuta & Henderson-Smart 1999) suggests that HFJV cannot be recommended for preterm infants with RDS. Lucey et al (2004) states that currently there are no randomised clinical trials on the interventions used on extremely premature infants, while Silverman (2003, p. 5) reminds us that “...the impatient let’s try-it-and-see approach in the burgeoning field of neonatal medicine has resulted in therapeutic disaster after disaster”. With enhanced technical competence have come the ethical dilemmas about the appropriateness of intervention with technology for the extremely premature infant.

2.3 Embryological development of the fetus

The transformation of the embryo to a fetus is a gradual process which has major developmental significance. This transition signifies that the embryo has developed into a recognisable human being (Moore & Persaud 1998, p. 108). The development during the fetal period is mainly associated with rapid growth of the organs in body, especially during the ninth to 16th weeks. The fetal weight gain during this time is rapid with the

fetal weight increasing from 14 grams at five weeks to 200 grams at 16 weeks (Moore & Persaud 1998, p. 109 & p. 112).

At 20 weeks gestation all the organs have developed but are going through maturation. The eyes and ears are formed. The kidney is producing urine. The liver is functioning, but the placenta eliminates and detoxify fetal waste products. The heart and electrical conduction system are functioning, and sinus rhythm is present (Crockett 1999, p. 210). Until eight weeks gestation all embryos are female. Sex differentiation occurs when testosterone is released that transforms the embryo into a male (Moore & Persaud 2003, p.307). There have been co-ordinated limb movements since 14 weeks, and the ossification of the skeleton has already occurred (Moore & Persaud 1998, p. 112). The tongue and taste buds are developed. Slow eye movements are detected, and scalp hair patterns are determined. By the end of the 16th week the fetus is more human in appearance because its eyes have moved into a normal anterior position. At 21 weeks the blink/startle response is present, however the eyelids are closed (fused) but generally open at 26 weeks. The infant born at 24 weeks gestation or less will have fused eyelids (Moore & Persaud 1998, p. 114).

During 17 to 20 weeks the mother has felt fetal movements. The skin is covered with vernix caseosa, a greasy substance that prevents the fetal skin from being damaged by the amniotic fluid. Lanugo, a fine downy hair helps to hold the vernix in place. The eyebrows and hair are present at 20 weeks gestation. Brown fat, a specialised adipose tissue which produces heat by oxidising fatty acids, is forming. The amount of brown fat increases towards term, therefore the infant of marginal viability will lack sufficient quantities of brown fat to maintain thermoregulation. This lack of brown fat will also give them a skeletal appearance (Moore & Persaud 1998, p. 114).

By the time the fetus has reached 24 weeks gestation, several major milestones have been reached. Head growth has started to slow down although it remains disproportionately large in comparison to the rest of the body. The external genitalia in both males and females has appeared. If the fetus is a female the uterus is formed and the ovaries contain

primordial follicles. If the fetus is a male the testes have begun to descend (Moore & Persuad 1998, p. 113). Fetal urine contributes to the amniotic fluid volume. The fetus is able to swallow the amniotic fluid. The intestinal coils have returned to the abdomen and the abdominal wall and diaphragm have closed. The eyes and ears are present. The face has a human profile. The fetus is able to feel pain because the cortical and thalamic areas are connected. The cerebral cortex is mature as evidenced by sustained burst patterns on EEG, which are present at 22 weeks gestation (Bildner 1999, p. 511). The fingernails are present at 24 weeks (Moore & Persuad 1998, p. 114).

2.4 Organ development

The development of the organs has occurred when the infant is born at 24 weeks gestation. Maturation makes the organs ready to function, and sustained function is essential for survival.

2.4.1 The lungs

If the lungs have not achieved a certain degree of maturity at birth, the infant is unable to survive regardless of the provision of NIC. Pulmonary maturity is defined by three components, the stage of anatomic development of the lung, the capacity to produce surfactant, and the neuromuscular drive to breathe (Hack & Fanaroff 1988, p. 773), all of which are governed by gestation. The major factors that determine the biologic limits of extrauterine fetal viability are the pulmonary alveolar immaturity and the availability of the fetal blood vessels to exchange gas. Immature alveolar cell structure and the proximity to pulmonary blood vessels are inadequate prior to 23 weeks gestation (Porter Gunderson & Pitts Burns 1995, p. 10). This relationship between the alveoli and the pulmonary circulation is the ultimate determining factor in relation to extrauterine survival. Therefore, prior to 24 weeks the lungs are physiologically unable to participate in gas exchange.

The fetal respiratory system has formed, but is undergoing maturation when the infant is born at 24 weeks gestation. Alveoli, the units responsible for gas exchange are not present until 24-26 weeks. Between 24-28 weeks there is differentiation into type I pneumocytes and type II pneumocytes, which are involved in surfactant production. Surfactant is a surface active agent which decreases surface tension, and is secreted from approximately 22 weeks, (Kelnar, Harvey & Simpson 1995, p. 168), and increases in quantity until term. Lamellar bodies appear in the type II cells between 24-28 weeks, and surfactant is stored in these structures. Surfactant production can be induced by prenatal steroid administration to the mother or surfactant instillation to the infant after birth, or preferably both.

2.4.2 The brain

The brain is the organ that will determine the postnatal potential of the fetus, therefore damage to the developing brain can be catastrophic. At 24 – 26 weeks gestation the cerebral cortex has received its full complement of neurons, however it is not until after 26 weeks that the neurons migrate into the cerebellum. At 24 weeks gestation the brain is a thin shell of tissue which surrounds the cerebral ventricles (Peterson, Vohr, Staib, Cannistraci, Dolberg, Schneider, Katz, Westerveld, Sparrow, Anderson, Duncan, Makuch, Gore & Ment 2000, p. 1939). Physiological stress at this stage can interrupt the maturational processes, and the effect on the brain will vary by region. The stress of premature birth will contribute to the long term cognitive deficits, seen in extremely premature infants. Peterson et al (2000, p. 1939) found that extremely premature birth was associated with reductions in brain volume. Their study found that at eight years of age the cortical volumes of preterm children were significantly smaller than the term infant controls. The areas affected included the cortex (integrates higher order mental functions, movement, visceral functions, perception and behavioural reactions), cerebellum (co-ordinating muscular movement), basal ganglia, (gray matter within each cerebral hemisphere) corpus callosum (connects the cerebral hemispheres) as well as cortical gray matter in the amygdala (frontal lobe) and hippocampus (lateral ventricle; part of the limbic system which is associated with emotions/feelings). Peterson et al

(2000, p. 1939) concluded that the transition from intrauterine to extrauterine life of an extremely premature infant can profoundly disrupt fetal brain development. Ajayi-Obe, Saeed, Cowan, Rutherford and Edwards (2000, p. 1162) found that the cerebral cortex of extremely premature infants had less cortical surface and was less complex than in infants born at term. They concluded that damage acquired during critical brain growth times may be permanent, because most growth in cortical connections and complexity occurs after 25 weeks gestation.

2.5 The extremely premature infant in the neonatal intensive care unit

Because blood is visible in the capillaries, the babies are red, tiny, and have a fetal appearance. The skin is wrinkled and translucent. Lanugo gives a hairy appearance. They look like a miniature version of a baby but lack the maturity of certain vital structures that enable extrauterine survival.

The NICU is frequently busy, bright and noisy and not the ideal environment for a newborn. It is in this environment that extremely premature infants will spend the first few months of their lives. McHaffie and Fowlie (1996, p. 1) suggest that what happens inside the NICU is so compelling that the outside world ceases to exist. The NICU becomes a place of infinite possibilities.

Extremely premature babies are nursed in incubators because they are unable to maintain their own thermal balance. The incubator may be humidified with condensation on the incubator walls. Immature non keratinized skin allows for large evaporative losses (Subramanian 2006, p. 2), and because of its fragility skin breakdown occurs. Humidity is important because it prevents fragile skin from drying out, cracking and peeling. The babies are prone to infections (Paxton 1999, p. 413) because of an immature or almost non-existent immune system. They may be jaundiced, the result of the destruction of red blood cells and liberation of bilirubin. The immature liver cannot process bilirubin as rapidly as it is made. It is hoped that the bilirubin does not cross the blood brain barrier and cause kernicterus (Subramanian 2006, p. 4). The babies have an endotracheal tube in

either their nose or mouth, and are attached to a ventilator that will do the majority of the breathing for them. They are unable to be fed because their gastro-intestinal (GIT) system is immature. A tube will be situated in their stomach to drain off the air that has been pushed in by the ventilator, as a consequence of ventilating the lungs. They will have minute lines that enter the umbilicus. One line will be in an umbilical artery to monitor their blood pressure and allow for blood to be sampled, while the other line will be situated in the umbilical vein and will deliver a dextrose fluid to maintain their blood sugar level. Fluid management is critical, because the immature kidneys cannot compensate for the large evaporative losses (Jones Wessel & Kleeman 1995, p. 71). All physiological parameters will be monitored.

Extremely premature babies do not like to be touched or disturbed. The central nervous system is functioning, but it is extremely sensitive to stimuli. Such stimuli can be overwhelming. A parent's gentle touch can feel painful (Humes 2000, p. 83). It can be extremely difficult for parents to see their baby looking so different from their expectation, and to see their baby being treated in the NICU. Procedures can precipitate a stress response that may cause the baby to suffer an intraventricular haemorrhage. Technology can help these babies, but it can be the cause of damage. Such damage may affect any or all organs, resulting in chronic medical problems, developmental problems, speech and language delays and behaviour disorders (Louch, 1999, p.788). As Humes (2000) points out, "in the NICU time does not heal all wounds. Beyond a certain point, the longer a baby stays here, the less likely he is to make it out" (p. 24).

2.6 Conditions affecting the extremely premature infant

All the organs of infants of 24 weeks gestation and less are present at birth, however they still grow and develop. It is because of this continued growth that the organs can suffer iatrogenic damage; damage induced by technology. Humes (2000) suggest that "caring for such micropremies isn't about helping them along so much as it is about forcing their bodies to do things nature never intended" (p. 19).

2.6.1 Respiratory Distress Syndrome (RDS)

Respiratory problems are the most frequently seen complications in extremely premature infants (Vargo & Wiltgen Trotter 1998, p. 23). These problems will present at birth because of the immature lung development, lack of surfactant, and the lack of neural control of breathing. Respiratory distress syndrome (RDS), known as hyaline membrane disease, is the most frequent cause of mortality and morbidity in the extremely premature infant. The lower the gestation the higher the incidence of the disease (Vargo & Wiltgen Trotter 1998, p. 23). RDS occurs due to the lack of surfactant in the immature lungs. Consequently atelectasis (collapsed lung) occurs, resulting in large areas of the lungs not ventilated, decreased lung volumes, decreased lung compliance (stiff lungs), decreased alveolar ventilation and an increased work of breathing. These changes result in hypoxaemia (low arterial PaO₂), hypercarbia (high arterial PaCO₂) and metabolic acidosis (Vargo & Wiltgen Trotter 1998, p. 25).

Infants at risk of surfactant deficiency are given surfactant replacement. Administration requires an endotracheal tube, so that the white, frothy surfactant can be instilled directly into the lungs. Multiple doses have been shown to be more effective than a single dose (Soll 1998, p. 1). Surfactant use in extremely premature infants is controversial. In premature infants of greater gestations there has been an appreciable decrease in mortality and morbidity associated with surfactant administration (Whyte et al. 1993, p. 1). Surfactant increases the survival and decreases the mortality rate in the first 48 hours among treated infants. At 23 to 24 weeks the survival rate increased from 33% to 59% as a result of surfactant therapy (Ferrara, Hoekstra et al. 1994, p. 120), however this has not been associated with a reduction in chronic lung disease (to be discussed later in this chapter) (Martin, Sosenko and Bancalari, cited in Klaus & Fanaroff 2001, p. 254), or a decrease in the morbidity associated with extreme prematurity.

It is anticipated that extremely premature infants will require assistance with ventilation when they are born, therefore they are intubated, given surfactant and ventilated from birth. Oxygen therapy and mechanical ventilation, with surfactant replacement remain the

cornerstones of treatment for surfactant deficiency. Unfortunately the barotrauma caused from positive pressure ventilation, and the free radical injury from the oxygen therapy put the extremely premature infant at risk for pulmonary air leak syndrome and chronic lung disease (Vargo & Wiltgen Trotter 1998, p. 32). This iatrogenic damage is often unavoidable.

2.6.2 Chronic lung disease or bronchopulmonary dysplasia (BPD)

Chronic lung disease (CLD) or bronchopulmonary dysplasia (BPD) is one of the most common sequelae of intensive care for extremely premature infants. BPD is almost exclusively seen in preterm infants (Bancalari, Abdenour, Feller & Gannon 1979, p. 819; Bancalari 1988, p. 43), and the incidence of CLD is inversely related to gestational age and weight. Although the incidence of BPD may not be rising, there is an increase in the number of extremely premature survivors, therefore there is an increase in the incidence of CLD.

With few exceptions all extremely premature infants will receive mechanical ventilation with intermittent positive pressure (IPPV) during the first days of life (Maguire 2004, p. 475). Acute barotrauma is seen as the most likely cause because BPD occurs in infants who survive IPPV. The main indication for ventilation in the extremely premature infant is acute respiratory failure due to RDS, but may also be indicated for pneumonia, patent ductus arteriosus, or apnoea of prematurity (Bancalari 1990, p. 43). In infants with severe respiratory failure it is difficult to separate the effect of positive pressure from other factors that influence the development of BPD (Bancalari 1990, p. 43). Once BPD has developed these infants require mechanical ventilation and oxygen therapy for weeks and even months. The trigger for the deterioration in lung function may be a bacterial or viral infection or heart failure secondary to a patent ductus arteriosus (PDA) (Bancalari 1990, p. 43).

Oxygen (O₂) toxicity is also one of the risk factors for the development of BPD. High concentrations of inspired oxygen can produce functional and morphological changes in

the lungs. During initial exposure to 100% O₂, the pulmonary changes are characterised by interstitial oedema and swelling of endothelial cells. This is followed by destruction of the type I alveolar cells (gas exchange occurs through these). With continued exposure to 100% O₂ there is hyperplasia of the type II alveolar cells (secrete pulmonary surfactant), with further destruction of the type I alveolar cells. There is marked interstitial oedema with increased cellular activity of the macrophages and fibroblasts. Bronchiolar changes are marked and consist of mucosal necrosis with metaplasia and proliferation of the bronchial epithelium with peribronchiolar oedema resulting in obstruction (Bancalari 1990, p. 43).

In BPD, pulmonary function is disrupted due to airway obstruction, fibrosis, emphysema and areas of collapse. Alveolar hypoventilation and carbon dioxide (CO₂) retention occurs due to an increase in dead space ventilation resulting from increased minute volumes and smaller tidal volume due to tachypnoea (Bancalari 1990, p. 43). Infants show a marked increase in airway resistance, a decrease in compliance which markedly increases their work of breathing. Some infants develop signs of right-sided heart failure secondary to pulmonary hypertension with cardiomegaly, hepatomegaly and fluid retention (Bancalari 1990, p. 43).

Infants with CLD may require ventilation and O₂ therapy for months, and continued home O₂ for months or even years following discharge. CLD is also associated with poor nutrition, poor growth, poor feeding, prolonged hospitalisation and episodes of nosocomial infections (Hack & Fanaroff 1999, p. 199). What is worrisome is that CLD is related to poor long-term cognitive outcome (Leonard, Picuch, Ballard & Cooper, 1994, p. 611).

The administration of postnatal steroids such as dexamethasone may reduce the risk of CLD, however steroids can cause hypertension, hyperglycaemia, gastrointestinal perforation and impairment of growth (Stark, Carlo, Tyson, Papile, Wright, Shankaran, Donovan, Oh, Bauer, Saha, Poole, Stoll, Fanaroff, Ehrenkranz, Korones & Stevenson 2001, p. 95), and poor neurodevelopmental outcome (Wilson-Costello et al. 2005, p.

1000) due to poor brain and head growth (Wood et al. 2005, p. F138). CLD usually resolves during infancy, however children with CLD have a high rate of re-hospitalisation (Lamarche-Vadel, Blondel, Truffert, Burguet, Cambonie, Selton, Arnaud, Lardennois, du Mazaubrun, Guyen, Mathis, Breart, Kaminski 2004, p. 1342).

2.6.3 Patent Ductus Arteriosus (PDA)

The ductus arteriosus (DA) is the fetal channel connecting the pulmonary artery to the aorta. When a full term infant is born there is an increase in arterial partial pressure of oxygen (PaO_2) as the infant establishes respiration. This causes constriction of the ductus arteriosus. Premature infants lack ductal smooth muscle, therefore patency is prolonged. In extremely premature infants there are still circulating prostaglandins, and during fetal life these ensure ductal patency. In premature infants the incidence is 8:1000 births, however the incidence is proportional to the gestation, with a higher incidence at the extreme edge of viability (Crockett 1999, p. 222). Untreated patent ductus arteriosus (PDA) can predispose the infant to CLD (Bhat & Zikos-Labropoulou 1986, p. 462). Indomethacin is the treatment for PDA and works by inhibiting prostaglandin synthesis (MIMS online 2003). Indomethacin has serious side effects. It can interfere with renal function, cause gastrointestinal bleeding leading to necrotising enterocolitis (NEC), and inhibit platelet function leading to intracerebral haemorrhage (Sadowski 2004, p. 608). The alternative to indomethacin is surgical ligation, but the fragility of extremely premature infants does not make them ideal candidates for anaesthesia.

2.6.4 Necrotising enterocolitis (NEC)

Necrotising enterocolitis (NEC) is an acquired, multifactorial disease which is a major cause of mortality and morbidity among the extremely premature infant population. The incidence is one to ten percent of all NICU admissions, and approximately 90% of cases involve premature infants (Watson 1999, p. 274). Premature infants are susceptible to NEC because of their intestinal immaturity. This immaturity results in decreased immunologic factors in the gastrointestinal tract (GIT), increased gastric pH, immature

intestinal barrier and decreased intestinal mobility (Watson 1999, p. 274). Gut ischaemia is a potential risk factor for NEC as blood is diverted away from the gut. Infection plays a prominent role in the development of NEC as bacterial colonisation occurs in the intestinal tract (Vasan & Gotoff 1994, p. 426). Enteral feeds have also been implicated in NEC, and 90-95% of infants who develop NEC have had enteral feeds (Watson 1999, p. 274). Enteral feeds provide a substrate for gas forming bacteria to multiply in the gut. NEC is characterised by areas of necrotic bowel, and can affect the bowel anywhere from the oesophagus to the anus, but most commonly affects the terminal ileum (Watson 1999, p. 274).

Spontaneous intestinal perforation has emerged as a new condition among extremely premature infants. It can be distinguished from NEC, but occurs much less frequently (Tatli, Kumral, Duman, Demir, Gurcu & Ozkan 2004, p. 999). Infants who spontaneously perforate their bowels, are generally smaller and more premature than those with NEC. The onset is likely to have been earlier than NEC and infants are likely to have been exposed to indomethacin (for patent ductus arteriosus), postnatal steroids (for chronic lung disease) or to have had a systemic candida infection (Fonaroff, cited in Klaus & Fanaroff 2001, p. 186) or presented in newborns whose mothers had been given indomethacin therapy for preterm labour (Norton, Merrill, Cooper, Kuller & Clyman, 1993, p. 1602).

Infants with NEC and intestinal perforation may develop “short gut/bowel syndrome” (Watson 1999, p. 276) where there is not enough intestine left to allow for the adequate functioning of the GIT. When the surgical team attempts to remove the necrosed portion, they find that there is no viable bowel. These infants cannot survive.

2.6.5 Retinopathy of prematurity (ROP)

Retinopathy of prematurity (ROP) is a developmental vascular disorder, leading to various degrees of vision loss and/or culminates in blindness (Phelps 1990, p. 63). ROP only occurs in infants whose retinal vessels have not yet completed their centrifugal

growth from the optic disc (Martin, Sosenko & Bancalari, cited in Klaus & Fanaroff, 2001, p. 248), therefore the condition predominantly occurs in premature infants. The degree of prematurity is the most important aetiologic factor for the development of ROP, and Phelps (1990, p. 63) suggests that most infants under 1000g have some degree of ROP. Milder stages of the disease may regress spontaneously and do not affect the normal development of the eye (Holmstrom 1993, p. 1). Other than gestation (less than 28 weeks) and birthweight (less than 1000 grams) the risk factors for ROP are multifactorial and include acidosis, shock, asphyxia, hypothermia, hypercarbia, hypocarbia, hypoxaemia, exposure to bright lights, vitamin E deficiency, and patent ductus arteriosus (Lee 1999, p. 31).

The retinal vessels which nourish the inner retina begin to grow from the optic nerve head at approximately 16 weeks gestation, and have reached the ora serrata by near term. ROP is an acute injury leading to the loss of newly developing retinal cells. After the vessels have been damaged the retina begins to grow new blood vessels from the few that remain. The vessel growth is driven by angiogenic factors released by the avascular retina (Phelps 1990, p. 64). ROP is seen as new vessels reaching towards the ora serrata in excessive numbers. A ridge of tissue also appears at the anterior edge of the new vessels and can give rise to vessels which leave the retina and penetrate the vitreous. The new vascular growth in most infants with ROP remains within the retina, however in some infants the retinal vessels become engorged and torturous. ROP can progress to retinal detachment. Infants with bilateral retinal detachments are most likely to be blind, however they may retain some light/dark perception.

ROP tends to surface as the infant's condition is improving (Lee 1999, p. 31), however, the sicker the infant the higher the risk of ROP. The number of complications experienced by an infant is strongly correlated with the incidence of severe ROP. ROP is rarely visible prior to 4 weeks after birth, but it progresses to the maximum severity by 17-20 weeks, after which time it regresses slowly (Flynn, Bancalari, Bachynski, Buckley, Bawol, Goldberg, Cassady, Schiffman, Feuer, Gillings, Sim & Roberts 1987a, p. 620). The visual outcome for infants with retinopathy can be anywhere on the spectrum from

mild to severe, with almost anything between myopia (near sightedness) on one end and detached retinas leading to blindness on the other end of the spectrum (Shapiro & Fraser Askin 1999, p. 614).

2.6.6 Periventricular - Intraventricular haemorrhage (P-IVH)

When extremely premature infants are born, the developing brain can be easily injured. These injuries are either as a result of disruption of the blood flow or lack of oxygen to specific areas of the brain. Bleeding from fragile blood vessels can impede the blood flow to uninjured areas (Carter 2001a, p. 1, Carter 2001b, p. 2). Alterations in cerebral blood flow and damage to the germinal matrix are believed to be responsible for the development of periventricular and intraventricular haemorrhage (P-IVH) (Paige & Carney 2002, p. 671). P-IVH occurs in 40-50% of infants less than 34 weeks gestation (Ment 1990, p. 19). Ischaemia increases capillary membrane permeability, but also decreases cerebral autoregulation, which can result in rapidly increased blood pressure and bleeding. Following IVH and germinal matrix haemorrhage (GMH) there is a markedly diminished cerebral blood flow (Ment 1990, p. 19).

The brain injury resulting from haemorrhages into the ventricles is a major cause of death in extremely premature infants (Vargo & Wiltgen Trotter 1998, p. 49), and almost half of the infants with major haemorrhages die. The most common site of origin of P-IVH in the preterm neonate is the subependymal germinal matrix (Vargo & Wiltgen Trotter 1998, p. 48), however a small number may originate from the choroid plexus (McCulloch 1999, p. 495). The subependymal germinal matrix is the primary source of neurons and glial cells for the developing brain (Vargo & Witgen Trotter 1998, p. 48), and damage to this area can be catastrophic. P-IVH may extend into the lateral ventricles, and when this occurs the blood fills the ventricles and obstructs the normal flow of cerebrospinal fluid (CSF) which causes dilation of the ventricles. Haemorrhage into the periventricular white matter is the most extensive type of P-IVH and it results in tissue destruction (Vargo & Wiltgen Trotter 1998, p. 48)

The risk factors for P-IVH include anything that can alter the cerebral blood flow in the extremely premature infant. This includes abrupt changes in blood pressure (hypo and hypertension), volume expansion, pneumothorax and hypercapnea (high levels of carbon dioxide in the blood) (Ment 1990, p. 19). Autoregulation is where the cerebral blood flow is constant over a wide range of systemic blood pressures. Autoregulation is impaired in premature infants (Vargo & Wiltgen Trotter 1998, p. 49), which makes them prone to IVH. Haemorrhages are graded according to the area where the bleed occurs. Grade I is an isolated germinal matrix haemorrhage, grade II is an IVH only, grade III is an IVH with ventricular dilatation and grade IV is an IVH with brain parenchymal haemorrhage (Vargo & Wiltgen Trotter 1998, p. 49). There is a correlation between the grade of bleed and the likelihood of the infant developing serious neurological sequelae (Paige & Carney 2002, p. 674). Grade III and IV haemorrhages are the worst types of haemorrhages and are associated with severe neurological sequelae and long term morbidity (Paige & Carney 2002, p. 674).

The onset of P-IVH is generally in the first six to eight postnatal hours, and almost all of the early haemorrhages are detectable within the first postnatal hour (Vohr, Allan, Scott, Katz, Schneider, Makuch & Ment 1999, p. 212). It is during the time that the infant is being resuscitated and stabilised that the damage is likely to occur. The brain of the extremely premature infant cannot be protected against bleeding into the ventricles. Providing treatment is a major contributing factor to the bleeding.

Intracranial lesions detected by ultrasound in the neonatal period affect the neuro-developmental prognosis of the infant (Aziz, Sauve, Etches, Pain, & Robertson 1995, p. 837). Infants with P-IVH or germinal matrix haemorrhage (GMH) are more likely to develop seizures and hydrocephalus, and have a higher mortality rate (Tucker Blackburn 1998, p. 587). Infants with brain parenchymal haemorrhage are at significant risk for poor neuro-developmental outcome (Papile, Munsick-Bruno & Schaefer, 1983, p. 273). Cerebral ventriculomegaly (dilatation of the cerebral ventricles) may reflect a loss of brain parenchyma and therefore the infant may be at risk of disability even if there is some recovery (Aziz et al. 1995, p. 837). The sequelae associated with P-IVH include spastic diplegia, spastic quadriplegia, hemiparesis on the opposite side of the

haemorrhage, post haemorrhagic hydrocephalus (which will require a ventriculo-peritoneal shunt to drain the CSF), learning disabilities and intellectual deficits (Vargo & Wiltgen Trotter 1998, p. 49). Hydrocephalus which requires shunting has been found to be a significant risk factor for both cerebral palsy and major cognitive deficits (Cherian, Whitelaw, Thoresen & Love 2004, p. 305), as well as a higher mortality and worse developmental outcome (Ward & Beachy 2003, p. 10). The severity of the initial P-IVH is positively correlated to the severity of the neurological damage and therefore outcome. Cerebellar infarction and atrophy have also been reported in extremely premature infants following P-IVH (Mercuri, He, Curati, Dubowitz, Cowan, Bydder 1997, p. 139). Children with early onset IVH with significant central nervous system injury are likely to have further decline in their cognitive function with increasing age (Ment, Vohr, Allan, Katz, Schneider, Westerveld, Duncan & Makuch 2003, p. 706).

There is still some uncertainty associated with ultrasound technology. Harrison (2002a, p. 1) suggests that changes in the amount of blood from P-IVHs can be detected by ultrasonography, however when blood is no longer detected, having been reabsorbed by the body, the haemorrhage is thought to be “resolved”. The difficulty is that because the blood has disappeared there is no guarantee that there will be no residual damage.

2.6.7 Periventricular Leukomalacia (PVL)

Periventricular leukomalacia (PVL) is a devastating neurological condition. Approximately 80-90% of PVL occurs in premature infants. PVL is an ischaemic lesion of arterial origin which makes the periventricular white matter necrotic. PVL therefore is cell death of the white matter (Carter 2001b, p. 2). It occurs when there is systemic hypoperfusion which is severe enough to interfere with the cerebral blood flow. The onset of PVL is after the first week of life. It is superior to, and lateral to, and immediately adjacent to the lateral ventricles. In PVL the ultrasound within a few weeks shows small cysts a few millimetres in diameter often bilateral that occasionally coalesce. The difference between P-IVH and PVL is the P-IVH is a haemorrhagic lesion and PVL is an ischaemic lesion. Extremely premature infants may have diffuse white matter

damage that is more extensive than the originally described PVL, and this damage may not be identified on ultrasonography (Aziz et al. 1995, p. 837; Hack & Taylor 2000, p. 1973). Cysts or holes in the brain which characterise PVL may form and then “cave in” with the surrounding brain tissue moving to fill the space. These cysts may disappear, however brain tissue is destroyed in the area where the cyst was located (Harrison 2002a, p. 2). White matter disease is associated with the development of cerebral atrophy and /or a reduction in cortical gray matter in preterm infants with PVL, by the time they reach term. The outcome for infants with PVL is spastic diplegia, intellectual deficits, upper and lower limb weaknesses and visual impairment (McCulloch 1999, p. 503).

2.6.8 Cerebral palsy

Neurological handicap can usually be detected in the later part of the first year, however severe defects will be noticed much earlier. Major neurological handicap is defined by Hack (cited in Klaus & Fanaroff, 2001, p. 530) as cerebral palsy (CP) which includes spastic diplegia, (similar parts on both sides affected) spastic quadriplegia, (all 4 limbs involved) spastic hemiplegia (one side of body affected) or paralysis, hydrocephalus, with or without CP or sensory deficits, blindness (ROP) or deafness. The intellectual potential of these survivors will differ, and will depend on their neurologic diagnosis. Children with spastic quadriplegia will have severe cognitive deficits, while children with spastic diplegia or hemiplegia may have relatively intact cerebral function (Hack, in Klaus & Fanaroff, 2001, p. 530). There is still much uncertainty associated with neurological prognosis as mental functioning may not be measurable until after two to three years of age (Hack, in Klaus & Fanaroff, 2001, p. 530).

CP is the term applied to disorders which are characterised by impaired movement and posture (Hockenberry 2003, p. 1834). For CP to be accurately described there must be motor impairment which stems from malfunction of the brain (Badawi, Watson, Petterson, Blair, Slee, Haan & Stanley 1998, p. 520). In CP there is difficulty transmitting impulses from the brain to the muscles which results in disruption of co-ordinated

movement. Difficulties with movement are part of the spectrum of CP. In the prematurely born infant the brain tissue most susceptible to injury includes the area surrounding the ventricles. The motor fibres which affect the legs run through this area, therefore damage to this area causes movement difficulties which primarily affect the legs (Carter 2001b, p. 2).

CP is the most common cause of permanent childhood disability (Australia & New Zealand Perinatal Societies 1995, p. 284; Hockenberry 2003, p. 1834). More extremely premature infants are surviving, which may account for an increased number of children with disabilities. Extremely premature infants with CP constitute only a small percentage of the overall number of disabled children. According to Carter (2001a, p. 1) approximately 10% of premature infants less than 1000 grams will be diagnosed with CP. Children with ELBW or gestational age are not the most at risk for the development of cerebral palsy. CP is found most often in infants with birth weight between 1250 and 1500g (Veelken et al. 1991, p. 815). This could mean that smaller infants with severe cerebral damage may have died, and heavier ones survived with handicap. There is much uncertainty about the diagnosis of CP, because half of all premature infants diagnosed with CP have normal NICU ultrasounds, and moreover half of the premature infants who leave NICU with a normal head ultrasound do not have normal brain magnetic resonance imaging (MRI) in adolescence (Harrison 2002a, p. 1). This finding is confirmed by Kitchen, Ford, Rickards, Doyle, Kelly and Murton (1990, p. 60) who found that several children with cerebral palsy at five years of age had no cerebral abnormalities detected on ultrasound during the neonatal period. This is disturbing because of the reliance on ultrasound technology in the neonatal intensive care to give indicators of prognosis and outcome.

2.7 The outcomes for babies of 24 weeks gestation and less

The majority of extremely premature infants who are born will die within the first two days. Macfarlane, Wood and Bennett (2003, p.F200) found that survival at 22 weeks gestation was a mean of 60 minutes, which increased to six hours for 23 weeks gestation.

Lucey et al (2004, p. 1559) found that 52% of infants less than 500 grams died in the delivery room. Increasing numbers of extremely premature infants are surviving (Lucey et al. 2004, p. 1559). For those who do survive, the outcomes are uncertain at best. This presents difficulties for those who do follow up studies, as the number of extremely premature infants are small, therefore the outcome data is also small and may not be generalisable. There is significant mortality rate variation between centres (Genzel-Boroviczeny et al. 2006, p. 71). Outcome studies can also be misleading because they may include the infants who have already died so that the disability outcomes may not appear to be as discouraging. The intact survival of fetal infants is uncommon (Lucey, 2004, p. 1819). Poor outcomes include global cognitive delay, CP, blindness and deafness. By school age these translate to decreased academic achievement, behavioural difficulties and inadequate social and adaptive functioning (Hack & Taylor 2000, p. 1973; Hack, Taylor, Drotar, Schluchter, Cartar, Andreias, Wilson-Costello & Klein 2005, p. 318).

When a premature baby is nursed in the NICU, the goals of parents and staff may be disparate. The goal of the NICU staff is survival of the neonate, and while survival is important to the parents, they are often more concerned about what the future will hold. When a tiny infant of 300 grams is admitted, staff may see this as a challenge and ask, “Will this be the smallest baby who has ever survived in our unit?” (Kirkley 1980, p. 873), and all of their efforts are directed towards that accomplishment. Kirkley (1980) suggests this is inappropriate because “no thought is given to the fact that it will probably die and the parents will have spent thousands of dollars for naught, or, worse still will have spent thousands of dollars and countless hours in anxiety only to have a less than normal child survive” (p. 873). Kirkley (1980, p. 873) has suggested that when damaged infants survive there are those who consider their presence not as a tribute to medical achievement, but as an accusation against misuse of medical power. Notwithstanding, there are some parents for whom this outcome is acceptable.

Problems exist with giving parents information about their baby’s possible prognosis and outcomes. Parents and medical staff might not be speaking the same language. Harrison

(2002b, p. 1) suggests that when medical staff use the term “OK” they are using it to talk about survival into childhood. Parents on the other hand use the term “OK” to mean the child will be normal. The term normal is also very subjective. To those who do the follow-up of these tiny infants, normal could mean an IQ over 72 and ambulatory, without severe disability or severe CP. Wolke and Myer (1999, p. 94) found that 50% of VLBW children, not even the ELBW cohort, had an IQ one to two standard deviations below their full term peers, as well as complex learning disabilities despite having an IQ>85. Although many children who were premature have an IQ above 72, their IQ is still considerably lower than their full term peers. According to Harrison (2002b, p. 1) the medical staff may view this child as normal, but this is not normal to the parents unless they have an IQ themselves of less than 85. When parents use the term “normal” they mean that the child will be indistinguishable from their full term peers, or how the child would have been had prematurity not interrupted its development (Harrison 2002b, p. 1). Parents of extremely premature babies may have no idea what outcome to expect for their child. Harrison (1983) herself a doctor and the mother of a premature baby wrote a book titled, *The premature baby book: A parent’s guide to coping and caring in the first years*. At the time there were no resources available to help parents deal with the aftermath of prematurity, and particularly what to do with the babies when they were taken home. Harrison (2002c) makes the point that medical staff may speak about the ongoing problems as being “mild”, however the problems do not seem to be mild for the parents or child who is struggling with them. Medical staff need to understand the outcomes of prematurity and how they will impact on the child and family, and not dismiss them as being mild. Literature to help the parents cope with what will lie ahead is extremely important as the levels of maternal education has been reported as a critical factor in the outcomes of tiny infants (Ambalavanan, Nelson, Alexander, Johnson, Biasini, Calo 2000, p. 501; Ward & Beachy 2003, p. 14)).

2.7.1 The problem with outcome studies

There is a dearth of literature on the outcomes of premature infants, however little of it addresses the population of 24 weeks gestation and less. Many studies report on birth

weight or gestation, and infants are grouped together as 23 – 28 weeks gestation, making it impossible to ascertain week specific estimates (Effer, Moutquin, Farine, Sagal, Nimrod, Kelly & Niyonsenga 2002, p. 743). The studies that exist are hampered by difficulties in tracking the infants over time, missing data, and they do not reflect the treatments that are currently available (Ward & Beachy 2003, p. 12). It is difficult to discover the evidence on which treatment decisions can be made.

There are problems with outcome studies as they exist. McCormick (1997, p. 869) believes that the purpose of outcome studies are too broad and vague and have inappropriate study designs. Present outcome studies provide little sense of the impact of the long term morbidity experienced by extremely premature infants. There is also evidence that nurses and physicians overestimate the severity of the negative outcomes, and this may influence parental choices (McCormick 1997, p. 871; Saigal, Stoskopf, Feeny, Furlong, Burrows, Rosenbaum & Hoult 1999, p. 1992; Blanco et al. 2005, p. e470). The outcomes for premature infants are often difficult to ascertain. Methodological problems including lack of standardisation of age at assessment, differing tests performed, and the use of referenced norms (Watts & Siagal 2006, p. F224), coupled with conflicting data make it difficult to draw conclusions about the outcome of extremely premature infants (Aylward 2003, p. 752). In a meta-analysis by Escobar (1992, p. 1) it was found that of the 1136 references to very low birth weight outcomes he could only identify 111 studies that were considered to be scientifically valid. Escobar (1992) also found that less than one third of the children were followed up for more than 12 months. This inability to report the full cohorts is not uncommon, and it means that children, especially those from lower socio-economic groups will be lost to follow-up, as parents from the group may not bring their children back for follow-up (Escobar 1992, p. 1). This has serious implications as many of the morbidities and disabilities do not present until after 12 months of age.

2.7.2 Disability

There is much debate in the literature about the disability rate for extremely premature infants and what constitutes a disability. The disability can be physical, cognitive, sensory or a combination of all of them. There are difficulties reporting on research because of the different definitions of disability and impairment severity (Watts & Saigal 2006, p. F223) used when researching surviving premature infants. Some suggest that the majority of premature infants who survive will be free of major disability (Lorenz, 2001, p. 348; Doyle and The Victorian Infant Collaborative Study Group 2004, p. 105; Vohr et al. 2005, p. 640; Mikkola et al. 2005, p. 1392), while others suggest that 50% or more of survivors will have a disability (Wood et al. 2000, p. 378; Rijken et al. 2003, p. 353). The incidence of disability and impairment has remained constant over the last decade (Vohr et al. 2005, p. 635), but the absolute numbers of infants with disability and impairments have increased (Lorenz, Wooliever, Jetton & Paneth, 1998, p. 425; Watts & Saigal 2006, p. F221). The subtle cognitive impairments that are seen in survivors without major disabilities (Aylward 2003, p. 752) remain a concern.

There are discrepancies in the outcome studies of extremely premature infants as they relate to disability. Battin et al (1998, p. 469) found that of the 23 to 25 week gestation infants in their study, 44 of the 47 were still alive. Thirty six percent of these children were impaired, and of those 38% had multiple impairments. This result is in contrast to Wood et al (2000) who found that 50% of extremely premature infants who survive have mental or physical disability, and 25% of those were severely disabled. Boys were affected more than girls. The Wood et al (2000) study showed a higher level of disability, but this may be because previous studies have failed to include such children as those who had functional disorders of the arms and legs, severe psychomotor delay and deafness or communication problems. These may not fit the criteria for disability that was used, but are nevertheless disabilities and should be classified as such. Even with NIC, including treatment with antenatal steroids, surfactant and dexamethasone, the incidence of major impairment has not improved for infants between 23 and 25 weeks gestation (Battin et al. 1998, p. 469; Augustines, Lin, Rumney, Lu, Bonebrake, Asrat & Nageotte 2000, p. 1113; Wilson-Costello et al. 2005, p. 997; Mikkola et al. 2005, p.

1391; Marlow et al. 2005, p. 9). Improvements in NIC techniques has increased the survival, but not improved the neurological outcome of extremely premature infants.

Surviving premature infants who are now adolescents and their parents have been interviewed, and the results show that even though they were disabled, the respondents viewed their lives as quite satisfactory (Saigal, Feeny, Rosenbaum, Furlong, Burrows & Stoskopf 1996, p. 454). Harrison (1996, p. 1722) suggests that in Saigal et al's (1996) research 61% of the survivors, some including those who were blind or non-ambulatory gave themselves perfect quality of life scores. Harrison (1996) who is a mother of a premature infant suggests that the "...positive attitudes the disabled and their families try to present in public can be colored with denial" (p. 1722). This would be an example of the able-bodied speaking on behalf of the disabled, but nevertheless it is difficult to get an accurate understanding, especially with the subjective nature of quality of life projections. The same ELBW survivors of Saigal et al (1996) are now adults and there has been some decline in the health related quality of life score in the last 10 years (Saigal, Stoskopf, Pinelli, Streiner, Hoult, Paneth & Goddeeris 2006, p. 1140).

2.7.3 Morbidity

Extremely premature infants who survive are likely to suffer severe morbidities or undesired complications. Morbidity increases with decreased gestational age and birthweight. The major morbidities which influence the outcome in later life are CLD, severe brain injury, NEC, acquired infections and ROP (Hack & Fanaroff, 1999 p. 199; Schmidt, Asztalos, Roberts, Robertson, Suave, Whitfield, & Trial of Indomethacin Prophylaxis in Preterms Investigators 2003, p. 1125). These morbidities are associated with high incidences of rehospitalisation (Kollee 2004, p. 1270; Lamarche-Vadel et al. 2004, p. 1340).

2.8 Conclusion

Infants born at the edge of viability are likely to have a multitude of problems, if they survive. It would appear that with current methods of neonatal intensive care, current survival, because of the stage of pulmonary biologic development, is 23 to 24 weeks gestation. With aggressive methods of neonatal care many infants initially do well and can be oxygenated adequately, however multisystem organ failure occurs and they succumb. Extremely premature infants have a high chance of dying early, and in children who survive there is the potential for significant morbidities, some which will have life long implications for these children and their families.

The rise in neonatal intensive care mirrors the rise in care of the premature infant. Neonatology remains a young profession in relation to the rest of medicine and much uncertainty exists. Science is able to answer many of the questions in relation to prematurity, but much of it remains an educated guess. It is these educated guesses that neonatal nurses must deal with in relation to caring for extremely premature infants. The following chapter will examine the ethical issues associated with caring for sick and damaged infants.