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OUTCOME BY BIRTHWEIGHT AND GESTATION AND FOLLOW-UP OF VERY LOW BIRTHWEIGHT INFANTS

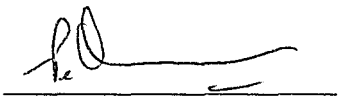
Peter Allan Cooper

A thesis submitted to the Faculty of Health Sciences, University of the Witwatersrand, in fulfilment of the requirements for the degree of Doctor of Philosophy

Johannesburg, 1999

DECLARATION

I, Peter Allan Cooper, declare that this thesis is my own work. It is being submitted for the Degree of Doctor of Philosophy in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at th. , or in any other University.



3rd day of March 1999

This thesis is dedicated to my wife Des, who has been a source of love and support throughout my professional career, to my children Nick and Simone who are part of a new generation of South Africans, and my parents Hilman and Kitty who have always 'been there'.

PUBLICATIONS AND PRESENTATIONS ARISING FROM THESE STUDIES

Publications

1. Cooper, P.A., Simchowitz, I.D., Sandler, D.L., Rothberg, A.D., Davies, V.A. and Wainer, S. (1994) Prevalence of hyaline membrane disease in black and white low-birth-weight infants. *S Afr Med J* **84**, 23-25. ***Received the Andries Blignault Award for the best multi-author paper in the South African Medical Journal in 1994.***

2. Sandler, D.L., Cooper, P.A., Bolton, K.D., Bental, R.Y. and Simchowitz, I.D. (1994) Periventricular-intraventricular haemorrhage in low-birth-weight infants at Baragwanath Hospital. *S Afr Med J* **84**, 26-29.

3. Shipalana, N., Cooper, P.A. and Strahlendorff, C. (1994) Early postnatal steroids for non-ventilated infants weighing less than 1000 g at birth - a randomised trial. *Pediatric Rev Commun* **8**, 29-33.

4. Cooper, P.A., Sandler, D.L., Simchowitz, I.D. and Galpin, J.S. (1997) Effects of suboptimal intrauterine growth on preterm infants between 30 and 32 weeks' gestation. *S Afr Med J* **87**, 314-318.

5. Cooper, P.A. and Sandler, D.L. (1997) Outcome of very low birth weight infants at 12 to 18 months of age in Soweto, South Africa. *Pediatrics* **99**, 537-544.

6. Cooper, P.A. (1999) Five year follow up of very low birthweight infants. *J Biosoc Sci* (submitted for publication).

7. Cooper, P.A., Bolton, K.D. and Saloojee, H. (1999) Survival of very low birthweight infants at Baragwanath Hospital since 1950. (Manuscript in preparation).

Presentations at Scientific Meetings (Presented by the author)

1. Incidence of hyaline membrane disease by weight and gestation in low birthweight black infants. *Presented at the 9th Conference on Priorities in Perinatal Care in South Africa*, March 1990; Golden Gate, South Africa.

2. Early follow-up of survivors <1500g at Baragwanath Hospital. *Presented at the 10th Conference on Priorities in Perinatal Care in South Africa*, March 1991; Eastern Transvaal, South Africa.

3. Long term follow up very low birthweight infants in a developing community. *Presented at the 13th Biennial Congress of the Nutrition Society of Southern Africa*, April 1992; Pretoria, South Africa.

4. Outcome to 1 year of very low birthweight infants in a developing community. *Presented at the International Symposium on Fetal and Neonatal Neurology*, October 1992; Tours, France.

5. Is the policy of not ventilating infants <1000g at birth appropriate? *Presented at the 13th Conference on Priorities in Perinatal Care in South Africa*, March 1993; Rustenburg, South Africa.

6. The effects of intrauterine growth retardation on hyaline membrane disease and intraventricular haemorrhage. *Presented at the 2nd Abbott Round Table Conference*, September 1993; Wilderness, South Africa.

7. Short and long term outcome of infants <1500g: Implications for health policy. *Presented at the 21st Biennial Congress of the Paediatric Association of South Africa*, August 1994; Eastern Transvaal, South Africa.

8. Long term outcome of very low birthweight infants. *Presented at the 3rd Abbott Round Table Conference*, September 1995; Drakensburg, South Africa.

9. Growth and development to age 6 years of very low birthweight infants. *Presented at the 16th Conference on Priorities in Perinatal Care in South Africa*, March 1997; Warmbaths, South Africa.

10. Short and long term effects of sub-optimal intrauterine growth of very low birthweight infants. *Presented at the 1st European South African Paediatric Congress*, March 1997; Johannesburg, South Africa.

11. Survival of very low birthweight infants in Johannesburg since 1950. *Presented at the International Congress of Paediatric Surgery and Paediatrics*, February 1998; Cape Town, South Africa.

ABSTRACT

Very low birthweight infants (birthweight <1500g) constitute fewer than 3% of all infants born. However, their contribution to infant mortality and childhood handicap is significant out of proportion to their numbers. Throughout the ages, the vast majority of these infants died soon after birth, but the 20th century has seen a remarkable improvement in the survival of such infants.

The beginnings of organised care of very low birthweight infants began in France in the late 19th century. Such care gradually became the norm in most developed countries, but further advances were sometimes associated with significant iatrogenic complications. The past 40 years have seen the development of neonatal intensive care units, organised regional perinatal care and a vastly improved understanding of the many problems faced by these infants. These have resulted in dramatic improvements in their mortality, but morbidity and handicap rates have remained largely unchanged. The care of very low birthweight infants in South Africa has attempted to follow that of developed countries, but has usually lagged some years behind with many limitations due to the lack of adequate resources.

This thesis is centred around a series of studies carried out largely on very low birthweight infants in the neonatal unit of Baragwanath Hospital. The results of these studies can be summarised as follows:

1. The mortality of very low birthweight infants at Baragwanath Hospital over the past 50 years has improved dramatically and continues to do so.
2. Black very low birthweight infants have a lower incidence of respiratory distress syndrome

than white infants of comparable gestation in Johannesburg.

3. Very low birthweight infants at Baragwanath Hospital have a relatively high incidence of intraventricular haemorrhage, largely as a result of sub-optimal perinatal care.
4. Postnatal administration of corticosteroids to infants <1000g at birth who are not usually offered mechanical ventilation is not beneficial.
5. Long term follow-up of very low birthweight infants discharged from Baragwanath show handicap rates similar to those reported in developed countries and catch up in growth appears ongoing.
6. Intrauterine growth retardation is extremely common in black very low birthweight infants but, although this appears partly responsible for the lower incidence of respiratory distress syndrome, it does not improve neonatal mortality and appears to be detrimental as regards longer term function.

Many of the ethical discussions that take place in developed countries around the care of very low birthweight infants are not of direct relevance to developing counties. However, on the basis of these studies and applying generally accepted ethical principles, it is argued that neonatal intensive care is appropriate to South Africa, but that rationing of such care is necessary due to the limitation of resources.

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The in-hospital parts of this series of studies would not have been possible without the contributions of Dan Sandler, Nancy Shipalana and Dave Simchowitz - I gratefully acknowledge their help.

Long term follow-up studies are difficult to conduct under ideal circumstances, but are particularly difficult in an environment such as Soweto. I should like to pay special tribute to Muriel Sefuba, who carefully counselled the parents about the importance of long term follow-up and spent many days travelling to a variety of places to find some of the infants. After her retirement, Harriet Khuzwayo and Francis Motshabi continued this painstaking process with success and their help is also gratefully acknowledged.

I should like to thank Alan Rothberg who supervised this thesis, but who has also been a source of inspiration to me throughout most of my paediatric career.

Finally I should like to pay tribute to the children who were the subjects of the long term follow-up study and their families. A number of them travelled from distances hundreds of kilometres away to keep appointments and they have, collectively, reassured me of the value of neonatal care.

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ABBREVIATIONS

AGA	Appropriate for gestational age
ANOVA	Analysis of variance
BR	Birthweight ratio
BBA	Born before arrival (at the hospital)
BTT	Birth To Ten (study)
CI	Confidence intervals
HIV	Human immunodeficiency virus
MDI	Mental developmental index (of the Bayley score)
NICU	Neonatal intensive care unit
pO2	Partial pressure of oxygen
pCO2	Partial pressure of carbon dioxide
PDI	Psychomotor developmental index (of the Bayley score)
PV-IVH	Periventricular-intraventricular haemorrhage
PVL	Periventricular leukomalacia
RDS	Respiratory distress syndrome
ROP	Retinopathy of prematurity
SGA	Small for gestational age
VLBW	Very low birthweight
WHO	World Health Organisation

Chapter 1

Introduction - Overview of Low Birthweight Infants

Concern and debate about infants who are very small at birth is a relatively recent phenomenon, both in medical settings and in society at large. Until the latter part of the 19th century, very few such infants survived, since the knowledge and means to keep them alive did not exist. Indeed, in certain societies in the ancient world, infants who appeared weak, deformed, small or premature at birth were often exposed to death (Cone, 1985, p3). However, over the past 100 years, the quality of the care and the management of such tiny babies has advanced rapidly. Initially the care of these babies was provided by the doctors and nurses responsible for the care of pregnant women. However, in more recent times the new specialty of neonatology has developed to provide an effective high-technology environment for these infants with specially trained doctors, nurses and other paramedical personnel to care for them. The improvement in outcome for these infants has been quite remarkable, but, as with any other area of medicine, rapid advances have also thrown up new challenges, new ethical debates and the need for continuing reassessment of what is being done.

1.1 Birthweight and Gestation

Infants are usually defined at the time of birth in terms of two broad parameters: their size which is expressed in terms of their mass or weight and the length of time that they have been

allowed to grow and develop in the mother's uterus which is expressed as the gestation. The birthweight is a relatively simple measure to perform provided that accurate weighing scales are available, but gestation may be more difficult to assess. The latter is measured in terms of the number of completed weeks that have elapsed since the first day of the mother's last menstrual period, since this is easier to define than the date of conception, provided the mother is sure of the date of her last menstrual period. Alternatively, antenatal sonar examination during the first trimester of pregnancy is able to date the pregnancy accurately. However, as frequently occurs, the date of the last menstrual period neither is known nor was an antenatal sonar done early enough to date the pregnancy accurately (Chamberlain *et al,* 1970; Hall *et al,* 1985). In these cases, scoring systems may be utilised to assess gestation, but these are not reliable in inexperienced hands and, even in ideal circumstances where scoring is performed by trained personnel, may only be accurate to within two weeks of the true gestation (Dubowitz *et al,* 1970; Ballard *et al,* 1979; Ballard *et al,* 1991).

The need to measure gestation accurately was not always appreciated. Prior to the 1960s it was assumed that all infants who were small at birth were premature, and prematurity was defined as an infant weighing 2500g or less at birth. However, by the early 1960s it was appreciated that low birthweight infants could be categorised into those who were born too early and could be called preterm, and those who were born too small and could be called growth retarded (Butler and Bonham, 1963). As later highlighted by Griffin (1993), the importance of distinguishing between them soon became evident since their neonatal problems were often different and evidence was accumulating to suggest that their long term outcome was also different. Since both gestation and birthweight are represented on a continuum, it should be appreciated that infants may be both preterm and growth retarded at birth. Thus

infants who fall below two standard deviations from the mean weight for their gestation are frequently referred to as small for gestational age (SGA), the term that will be used in this thesis, and may be preterm, term or postterm (Battaglia and Lubchenco, 1967).

More recently the concept of the birthweight ratio has been introduced as a method of relating the infant's birthweight to his/her gestational age (Morley *et al*, 1990; Brownlee *et al*, 1991). It is calculated by dividing the birthweight by the median reference weight for that gestational age. The main advantage over the more conventional categorical method of classifying infants is that the birthweight ratio is a continuous numerical variable that can be handled in statistical analysis. It thus may provide a more sensitive method of studying the effects of impaired intrauterine growth, since using a continuous variable allows for degrees of growth retardation to be analysed rather than a categorical classification of above or below two standard deviations from the mean.

1.2 Definitions of Low Birthweight and Prematurity

Although both the birthweight and gestation can be measured accurately as discussed above, the definitions of what constitute normality is more complex. There are many factors that determine the normal distribution of birthweight in a given population. These include genetic determinants, environmental and nutritional factors, gender, altitude at which the population is living and the general health of the population over several generations as only some of the factors involved. Thus many different intrauterine growth curves have been derived, all with differing upper and lower cutoff values. However, in order to provide an international

standard, the World Health Organisation (WHO) recommended that infants should be classified as having low birthweight if they are born weighing less than 2500g (WHO, 1975).

While it is generally accepted that the median period of gestation is 40 weeks or 280 days with a standard deviation of one week, the lower limit of 'normal' has also been the subject of much debate. Once again the WHO made a recommendation in the interests of international standardisation, namely that preterm birth should be defined as the birth of any infant before 37 weeks gestation or less than 259 days since the first day of the last menstrual period (WHO, 1977). While there may be scientific and statistical arguments against this definition since the upper limit of gestation was given as 293 days which is only 13 days above the median compared with 21 days below the median for the lower limit, it is a practical one in the sense that it defines functional maturity of an infant in the sense that infants who have reached 37 weeks of gestation rarely develop any of the complications usually associated with prematurity.

1.3 The Importance of Very Low Birthweight

Since birthweight is the easier of the two parameters to measure, it has generally been more widely used and has long been recognised throughout the world as one of the major determinants of neonatal mortality. For example, it was recognised a number of years ago that, in the United States, low birthweight infants accounted for two-thirds of all neonatal deaths (Shapiro *et al,* 1968). However, infants who fall within this broad category of low birthweight actually constitute a number of diverse groups. The infant born at 24 weeks of

gestation weighing 500g, the infant born at 34 weeks gestation who is either well grown weighing 2000g or growth retarded weighing 1200g and the infant who is born at term but is marginally undergrown all fall into the same category of low birthweight. In order to define those at greater risk, those with a birthweight less than 1500g are generally referred to as having very low birthweight (VLBW). It was estimated that this latter group, which constituted just over 1% of all births, accounted for half of all neonatal deaths in the United States (McCormick, 1985), while the group of infants with birthweight 1500g to 2500g who constituted about 6% of all births accounted only for about 17% of all neonatal deaths. In more recent years, as more infants less than 1000g at birth have been surviving in developed countries, a new term of extremely low birthweight infants has been introduced to describe these infants.

In developing countries, the majority of infants with birthweight between 1500g and 2500g are SGA (Stein and Ellis, 1974) and therefore do not have major organ immaturity as commonly as those in developed countries and thus require the support of modern day intensive care units less frequently. Therefore, provided these infants can be offered a warm environment, oxygen and other forms of supportive care, they generally have a good prognosis for survival beyond the neonatal period. On the other hand, VLBW infants constitute a much higher risk group in the same way that they do in developed countries. Furthermore, intensive care facilities are usually available to a far lesser extent in developing countries (and frequently not at all) than is the case in developed countries, further accentuating the vulnerability of VLBW infants in developing countries.

Neonatal survival, however, is not the only factor to be considered when assessing the overall

outcome of low birthweight infants. Low birthweight infants also have a higher postneonatal mortality as a result of the complications resulting from low birthweight as well as the underlying socioeconomic factors that contribute both to a higher low birthweight rate and an increased infant mortality regardless of birthweight. Of equal concern is the contribution of low birthweight to morbidity in childhood. It was estimated by Hardy *et al* (1979) that, prior to the advent of modern intensive care, low birthweight infants were three times more likely than infants of normal birthweight to have neurodevelopmental problems, while, for those with very low birthweight, the risk was ten times greater. In spite of major improvements in neonatal survival of low birthweight and especially VLBW infants over several decades, the relative risk of neurodevelopmental handicap in surviving low birthweight infants compared with infants of normal birthweight did not appear to have changed (McCormick, 1985).

1.4 Low Birthweight Rates

Rates of low birthweight vary greatly throughout the world. As will be discussed in the next section on causes of low birthweight, these variations correlate largely with differences in socioeconomic conditions, but it remains unclear whether these variations are also influenced by genetic factors. These differences in low birthweight rates also fail to reveal differences in the rates of prematurity versus intrauterine growth retardation in making up the overall numbers of low birthweight infants. As mentioned above, the majority of larger low birthweight infants born in developing countries are SGA. In a study by Villar and Belizan (1982), comparison of international data sets revealed that most low birthweight infants born in developing countries were born at term and were therefore growth retarded, while more low

birthweight infants born in developed countries were premature. Similarly the low birthweight rates in developing countries correlated with the numbers of infants with intrauterine growth retardation and not with the numbers of those born prematurely whereas the opposite was true for developed countries. The divide appeared to occur with low birthweight rates approximating 10%.

The WHO has accumulated data on low birthweight rates throughout the world and the most recent figures available are those for the period 1990-1994 (Bellamy, 1998). These are shown in Table 1.1.

Table 1.1: Low birthweight rates (%) for different regions of the world

Region	Low Birthweight Rate
Sub-Saharan Africa	16
Middle East & North Africa	11
South Asia	33
East Africa & Pacific	11
Latin America & Caribbean	10
Industrialised Countries	6
All Developing Countries	18
World	17

The enormous differences in the rates of low birthweight are evident from this table. In industrialised countries only 6% of infants born weigh less than 2500g with some countries such as Norway having a rate of 4%, while in South Asia fully one-third of all infants are born below this weight.

1.5 Causes of Low Birthweight

Lists of risk factors for and causes of low birthweight are given in most standards texts of obstetrics and neonatology. However, it is often unclear how these factors interact with each other and a coherent classification of the causes has been attempted by many authors. In his comprehensive review of the literature, Rothberg (1991) classified the factors into four broad areas: constitutional factors, nonspecific maternal factors, factors associated with reduced uteroplacental blood flow, and disorders of the placenta, membranes and cervix. These will be summarised briefly.

1.5.1 Constitutional Factors

These factors include ethnicity, maternal stature, fetal gender, multiple births and congenital abnormalities. As shown in the international comparisons above, there are marked differences in the incidence of low birthweight in different parts of the world and these differences are largely related to the vast socioeconomic differences that exist between different regions of the world. However, it is not clear why there should be substantially higher rates in South Asia as compared with Sub-Saharan Africa while markers of broad socioeconomic conditions appear to be relatively similar. Ethnic differences due to differing genetic determinants have therefore been postulated, but other factors such as diet and lifestyle may be more important in explaining the observed differences. Similarly, the birthweight distribution of Japanese infants born in the United States appears to mimic that of infants born in Japan rather than that of infants born to mothers of comparable socioeconomic status in the United States (Evans *et al,* 1989), but once again the effects of diet and lifestyle cannot be separated.

There is a positive correlation between maternal height and indeed the mother's own birthweight with the birthweight of their offspring (Klebanoff *et al,*1984). The smaller the mothers, the higher the proportion of low birthweight infants they have. This however, was shown to be mediated more through a limitation of fetal growth than a curtailment of gestational age, though both contribute to the overall effect (Chamberlain *et al,* 1975). Maternal stature is itself determined by a variety of factors both genetic and environmental and the secular trend in the increase in adult stature over the past 150 years in developed countries suggests that several generations of adequate nutrition and favourable environmental conditions are necessary to obtain the full genetic potential of adult stature (Kaplan, 1991). Secular trends in birthweight appear to follow similar patterns (Nestlé Nutrition Workshop Series, 1981).

The most consistent genetic influence on birthweight is exerted by the gender of the fetus. Male gender appears to enhance growth in the fetus and thus reduces the rate of low birthweight. However, the lower birthweight of female infants is not associated with a higher risk of mortality; in fact the reverse is true (Naeye and Tafari, 1983). Multiple pregnancy also exerts a very powerful effect on birthweight distribution and this is due both to the adverse effects on fetal growth and the higher rates of preterm delivery (Alberman and Evans, 1989).

Congenital abnormalities, whether of chromosomal or non-chromosomal origin, will affect the birthweight distribution adversely. Similarly, chronic intrauterine infections with organisms such as rubella, cytomegalovirus, toxoplasmosis and syphilis will affect intrauterine growth and development adversely. Congenital syphilis in particular was a major cause of premature delivery in developed countries less than 100 years ago and was estimated to be a contributing

factor in more than 50% of cases of premature delivery in developed countries at that time (Cone, 1985, p47). Naeye and Tafari (1983) indicated that it remains an important cause of perinatal morbidity and mortality in many developing countries and Venter *et al* (1987) have confirmed that it is still an important cause of low birthweight and perinatal wastage in South Africa. Other factors known to cause low birthweight include intrauterine exposure to agents such as alcohol (Jones and Smith, 1975).

1.5.2 Non-Specific Interactive Maternal Factors

These include a number of factors that are regarded as important in determining birthweight and duration of pregnancy. However many of these factors coexist and interact with each other making it extremely difficult to identify any one of them as an independent cause of low birthweight or preterm delivery. Socioeconomic status appears to be associated very strongly with birthweight distribution. The differences in low birthweight rates in different parts of the world as illustrated above do follow socioeconomic differences in broad terms. Similarly previous studies in Britain have shown an increasing rate of low birthweight as social class changes (Butler and Alberman, 1969). However, social class is closely associated with maternal stature and the British perinatal mortality survey showed that the effect of social class on birthweight was no longer significant once maternal stature was taken into account. Socioeconomic status is also closely associated with nutrition. However, the nutritional status of the mother during pregnancy does not seem to play an important role in determining birthweight unless it is severely compromised. Indeed we were unable to show an effect of nutritional supplementation on a cohort of pregnant women from poor socioeconomic conditions in South Africa (Cooper *et al,* 1991). This cohort was, however, not acutely

malnourished and, due to the fact that commencement of antenatal attendance in this population was usually relatively late, supplementation could only be initiated in the third trimester.

Factors such as birth order and maternal age are also associated with birthweight (Alberman and Evans, 1989). First born infants generally have lower birthweights than second and third births, but increasing parity beyond the fourth pregnancy is once again associated with lower birthweight. Similarly very young and very old mothers appear to have infants of lower birthweight, but it is once again difficult to separate out these factors from the complex socioeconomic markers with which they are often associated. For example, poorer women often have their first pregnancy during their teenage years, but are also more likely to become grand multiparous mothers and are thus overrepresented at both ends of the maternal age spectrum.

Other factors such as previous pregnancy outcome, short inter-pregnancy interval, work during pregnancy, prenatal care and marital status have all been implicated in affecting the birthweight distribution and low birthweight rates. However all of them are once again closely related to socioeconomic factors and it is extremely difficult to implicate them as having an independent effect on birthweight.

Maternal stress has also been implicated in playing an important role in the genesis of placental dysfunction and preterm labour. The hypothesis of Bragonier et al (1984) is that stress results in the activation of interrelated hormonal and biochemical pathways that in turn result in decreased placental blood flow. These in turn may retard the growth of the fetus as

well as mediate uterine irritability and cervical changes that may result in premature labour.

1.5.3 Factors Associated with Reduced Uteroplacental Blood Flow

While some of the factors discussed in the preceding section may be associated with reduced uteroplacental blood flow, this is largely speculative. There is, however, more evidence to link factors such as maternal smoking, high altitude and maternal disease to reduced uteroplacental blood flow which in turn affects fetal growth adversely.

The damaging effects of maternal smoking have long been recognised, increasing the risk of intrauterine growth retardation, prematurity, stillbirth and neonatal death. Mechanisms for the effects of maternal smoking include abnormal placental histology and decreased intervillous blood flow (Meyer and Tonascia, 1977) with the result that the incidence of abruptio placentae, placenta previa and premature rupture of the membranes are all increased.

Babies born at high altitude have a lower weight for gestational age irrespective of ethnic group or other characteristics (Alberman and Evans, 1989) and this appears to be mediated by reduced uteroplacental blood flow. This is of relevance to births in Johannesburg with an altitude of 1700-1800m above sea level. In addition, certain maternal illnesses such as chronic hypertensive disorders, pregnancy-induced hypertension, renal disease and cyanotic heart disease all appear to affect fetal growth by causing reduced uterine perfusion.

1.5.4 Disorders of the Placenta, Membranes and Cervix

This category includes abruptio placentae, amniotic fluid infection and incompetent cervix. While the factors associated with abruptio placentae are complex, there is a strong association with abnormal placental blood flow and thus factors such as maternal smoking and hypertension are associated with this condition. Amniotic fluid infection, usually a result of pathogenic bacteria ascending from the vagina and cervix, is one of the more powerful predictors of fetal and neonatal deaths, most commonly as a result of the early initiation of labour resulting in preterm delivery (Naeye and Peters, 1978). Incompetence of the cervix, a condition in which the cervix matures, softens and dilates without apparent uterine contractions, can result in premature delivery. However, this would appear to be associated with only a small number of all the cases of low birthweight.

1.5.5 Causes of VLBW

As discussed previously, low birthweight is associated with infants who are growth retarded in utero or who are delivered prematurely or both. Clearly there is a continuum as regards both of these factors from mild growth retardation or borderline prematurity to the extremes of viability and it is logical to assume that the causes are similar across the entire range of the spectrum. However, it has been noted in the United States that in spite of all that has been learned about the causes of low birthweight, the incidence of deliveries of VLBW infants has increased over the past few decades (McCormick, 1994). This has raised the question as to whether there may be differences in the causes of VLBW delivery as compared with those of larger low birth weight infants (Wilcox and Russell, 1983).

1.6 Low Birthweight Infants in South Africa

The South African population is very diverse and, in many respects reflects in microcosm the diversity of the world's population. It is therefore not surprising that the profile of low birthweight infants in South Africa reflects this diversity. Of the population of approximately 40 million, more than 70% are made up of the original black (African) inhabitants of the country, about 14% are whites who originated largely from Western Europe with the first settlers arriving in the mid-17th century, about 10% are people of mixed race and 3% are made up of people who came from the Indian subcontinent mainly during the early part of the 20th century. In terms of the old political order that ruled South Africa until recently, each person was categorised into one of these four groupings and economic opportunity, area of residence, social services and health care were all strictly regulated accordingly. Culture, lifestyle and dietary habits also broadly followed these categories, although there were and still are many subgroups within the four broad groupings and much blurring of the margins and overlapping of groups. However, since health status still clearly reflects the past political and economic order, categorisation of the current population of the country into these four broad groups is still widely practised. Since the main focus of this dissertation is to investigate the VLBW profile of black infants in South Africa, these terms will be used where appropriate. Although a debate continues as to what are the most appropriate terms to use in South Africa, the terms that appear to be most widely used and accepted will be applied, namely black, white, mixed race and Asian.

In socioeconomic terms, white South Africans have historically had a lifestyle similar to that of the developed countries of the world, while black South Africans have been severely

disadvantaged. Asians and those of mixed race have occupied an intermediate position and health statistics have reflected these differences. No national birthweight statistics have been kept in South Africa, but some of the larger cities did collect data on birthweight. Statistics for 1988 from the Johannesburg Medical Officer of Health (Annual Report, 1988), one of the last years for which racially separate statistics were produced, showed that whites had a low birthweight rate of 8.6% while the figure for blacks was 16.4%. The figure for whites is similar to, but somewhat higher than that for industrialised countries in general and Western European countries in particular - the explanation for this is not clear. On the other hand the low birthweight rate of black South Africans is similar to the figure for Sub-Saharan Africa. The data available for those of mixed race and Asians indicates that their low birthweight rates are similar to those of black South Africans.

1.7 Prevention of Low Birthweight

As discussed previously, low birthweight is strongly associated with infant mortality and those that survive frequently require expensive forms of therapy to ensure their survival. In addition, a significant number of survivors have long term disability and handicap adding to the overall cost of their care as well as imposing a substantial social burden on their families and society. Thus, prevention of low birthweight would appear to be the obvious priority. However, in spite of all that is known about the causes of low birthweight, as indicated in the preceding section, many of these factors are interrelated and it is extremely difficult to unravel them. Indeed in the case of the individual woman who has a low birthweight infant, it is often impossible to find a specific preventable factor.

One of the factors most strongly associated with low birthweight is the lack of or inadequate attendance at antenatal clinic (Kliegman *et al,* 1990). However, once again there are many confounders associated with antenatal clinic attendance. Women who attend early and regularly often come from higher social classes, are healthier and have better access to health care. On the other hand, women who deliver prematurely have less time in which to receive antenatal care. This is especially important in the South African context where first attendance at antenatal clinic is frequently in the third trimester of pregnancy (Herman, 1987). Thus, inadequate or non-attendance at antenatal clinic may be a consequence of rather than a cause of prematurity.

It is also not clear what precise content and quantity of antenatal care are necessary to reduce low birthweight. There is no doubt that detection of specific problems in the mother such as syphilis and the treatment thereof will prevent a significant number of premature deliveries and indeed perinatal deaths. Detection of maternal hypertension and episodes of urinary tract infections and appropriate management thereof will affect the number of prematurely delivered infants and, in the cases where premature delivery is unavoidable, will improve the health status of the infant at birth (Kliegman *et al,* 1990). However, attempts at designating women for being at high or low risk for delivering low birthweight infants have not been very successful. In their overview of a number of studies, Alexander and Keirse (1989) concluded that only 10% to 30% of women designated for being at high risk actually experienced the predicted adverse outcome, while 20% to 50% of women who delivered preterm or low birthweight infants had low risk scores. Furthermore, even in those women who are recognised to be at high risk for delivering a preterm or low birthweight infant, it is often not possible to ensure delivery of infants at term and of normal birthweight, e.g. women with

severe maternal hypertension, multiple pregnancy.

Socioeconomic status remains as one of the major determinants of low birthweight with its interrelationship with nutrition and lifestyle. However, in the context of most developing countries with high rates of low birthweight, this is not amenable to short term intervention. Even in the United States this has not occurred. In 1979 the United States Public Health Service published the "1990 Health Objectives for the Nation" and one of the main objectives was to achieve a significant reduction of the low birthweight rate. However, no reduction was achieved and indeed the VLBW rate increased over the subsequent decade (Public Health Service, 1988). In their review Kliegman *et al* (1990) concluded that coordinated research activities should first be conducted before any new public programmes were initiated in an attempt to identify the specific social and biological variables associated with low birthweight more precisely.

One of the few programmes that did reduce the incidence of preterm births was described by Papiernik *et al* (1985) in France. This programme included identifying modifiable risk factors in pregnant women, both medical and lifestyle, a strong education programme to both pregnant women and their care-givers, as well as socially related legislation to reduce physical effort by pregnant women. This approach is considered to have been responsible for a decrease in the rate of preterm births from 6.3% to 4.2% between 1971 and 1982 in Haguenau, France.

Thus it would seem that reduction in the rate of preterm delivery and low birthweight is possible, but that it requires a coordinated approach involving the deliverers of health care as well as the resources to modify the lifestyle and activities of pregnant women in the broader

social environment. In the context of the realities of perinatal care in South Africa, however, such an approach would not be feasible (Dobbelaere *et al,* 1996). In the longer term, improvements in socioeconomic conditions and nutrition, probably over several generations, will be necessary to have a lasting impact on these low birthweight rates. In the meantime, in both industrialised and developing countries, low birthweight and especially VLBW infants will need to be cared for in significant numbers and they will continue to contribute substantially to infant mortality and later handicap. A proper understanding of their disease profiles, optimal management of their complications according to the resources available, and provision for adequate care of those that do not survive intact is therefore essential.

1.8 Ethical Considerations Regarding Low Birthweight Infants

Prior to the latter part of the 19th century, premature infants were usually referred to as weaklings or 'congenitally disabled' and elicited little attention. The pioneering work of Budin in France and others as described by Cone (1985, pp13-41) during the last two to three decades of the 19th century resulted in a remarkable improvement in the outcome of these infants. However, even at the beginning of the 20th century, the care of the premature infant in Britain and the United States lagged far behind, accompanied by attitudes that more active care was not warranted except in selected cases (Cone, 1985, p43).

Since then attitudes have changed completely, but ethical debates continue to be central to issues surrounding the care of premature infants. These ethical issues frequently invoke philosophical arguments around the rights of and what is best for the individual child in the

context of the family and society. However, the costs of care and limitations of resources are major considerations in all countries, but are especially so in developing countries where the gap between what is possible and what is affordable is greatest. Thus no thesis on the care and outcome of VLBW infants would be complete without addressing some of these ethical issues in the context of the practical realities in which such care is practised.

Chapter 2

Data from Developed Countries

Preamble

This chapter describes the advances that have taken place with respect to the care of VLBW infants over the past 100 years. From the beginnings of organised care of such infants in France towards the end of the last century, the advances in care that occurred during the middle part of the 20th century together with some of the iatrogenic complications are described. These developments foreshadowed the development of neonatal intensive care units in the 1960s and 1970s which incorporated major technological advances. Further advances in the care of VLBW infants over the past 20 years are also highlighted. The dramatic improvements in the mortality of VLBW infants as a result of all of these developments are described, but the effects on the morbidity and handicap rates of these infants are also examined.

2.1 Early Developments of Care of the VLBW Infant

As mentioned in the first chapter, VLBW infants historically had an extremely high mortality and it is probable that there were only occasional survivors of such infants prior to modern times. The basis of modern day neonatology began in the last two to three decades of the 19th century in France under the leadership of two French physicians, Tarnier and Budin. It would appear that their interest in the welfare of the premature infant was not motivated entirely by

humanitarian concerns, but was also influenced by the declining birth rate in France at that time and the extremely high infant mortality which was estimated to be 223 per thousand registered births (Cone, 1985, p15). Since France had recently been defeated in the Franco-Prussian war (1870-1871), there was concern that France's military strength would be severely disadvantaged in comparison with the potentially larger future German army! The major innovations introduced by Tarnier and Budin were:

1. Adequate means of keeping premature infants warm resulting in the development of primitive incubators.
2. Effective methods of feeding infants who were too premature to coordinate sucking and swallowing with gavage feeding as one of the major developments.
3. Strategies to prevent infection in premature infants.

Although some of these methods had been used on individual infants in the past, this was the first time that it was done in an organised institutional manner on large numbers of infants. With these relatively simple methods of caring for low birthweight infants, remarkable improvements in survival were noted. At one maternity hospital in Paris, the mortality of infants less than 2000g at birth fell from 66% to 38% over a two year period after the introduction of incubators (Tarnier, 1885 as quoted in Cone, 1985, p37)

Although some countries in Europe, notably Germany, developed methods of care for premature infants along similar lines, other countries such as Britain and the United States were slow to introduce similar institutionalised care. However, this gradually changed and, in the first half of the 20th century, patterns of care for VLBW infants developed in Europe

and North America that were based on principles described by Budin and Tarnier.

2.2 Further Developments and Iatrogenic Complications

The next major advances occurred in the 1940s and 1950s. Since many premature infants developed severe respiratory disease, administration of oxygen became more widely used in the care of VLBW infants. As previously mentioned in Chapter 1, syphilis was among the most important factors producing premature birth and, prior to the introduction of penicillin, almost all premature infants with signs of congenital syphilis at birth died (Cone, 1985, p57). However, as penicillin became more widely available over this time, both mothers and infants could be effectively treated. Incubators became more sophisticated and could deliver warmth and humidity in a controlled manner and newer and more effective techniques for feeding VLBW infants became available with the introduction of indwelling nasogastric tubes in the 1950s.

However, along with these came a number of iatrogenic complications. Perhaps the best known of these was the condition of retrolental fibroplasia or retinopathy of prematurity (ROP) which was produced in VLBW infants who were exposed to excessive concentrations of oxygen. Oxygen had been administered to infants from the 18th century, but it did not become common practice until the 1930s and 1940s (Cone, 1985, p67). Numerous devices were developed to administer oxygen in high concentrations to neonates and premature infants in particular, with the result that unrestricted concentrations of oxygen were administered to large numbers of susceptible infants. In 1948 a United States Government publication recommended that oxygen should be given for "respiratory difficulties, cyanosis from any

cause, and a general feeble condition" and some authorities even recommended giving oxygen to all very small premature infants (as quoted by Cone, 1985, p68). The first description of ROP was by Terry (1942) and an epidemic of blindness was documented in surviving premature infants over the next decade. Many potential causes of ROP were advanced until several controlled studies in the early 1950s showed unequivocally that unrestricted use of high concentrations of oxygen was associated with a significantly higher incidence of ROP. Once the results of these studies were published in the mid-1950s, the use of oxygen was restricted to those infants with clinical indication for its use and subsequent recommendations warned against giving oxygen concentrations of greater than 40%. As described by Silverman (1980), while the epidemic of ROP came to a dramatic halt, the other observation of the controlled studies, namely that mortality of VLBW infants was increased when oxygen was restricted, was not given widespread publicity. Avery and Oppenheimer (1960) suggested that the increase in perinatal mortality in the United States in the years after 1955 was due at least in part to the practice of restrictive oxygen therapy and McDonald (1963) described an increase in neurological handicap in ex-premature infants as a result of this practice. Only later, however, was it fully appreciated that the mortality of VLBW infants increased significantly as a result of the practice of restricting oxygen as did the number of neurologically damaged survivors due to the results of hypoxemia suffered by surviving infants (Hack *et al*, 1979).

2.3 Development of the Neonatal Intensive Care Unit

During the 1960s advances in knowledge about normal physiology resulted in a better understanding of the pathophysiology of certain neonatal conditions (Dawes, 1968). With

respect to VLBW infants, this resulted in more effective management of birth asphyxia including the use of early endotracheal intubation for resuscitation and a more scientific approach to the provision of fluids, electrolytes and calories so that the frequency of metabolic problems such as dehydration, acidosis, hypoglycaemia and hyperbilirubinaemia were reduced. As described by Hack *et al* (1979), major technological advances in bioengineering and biochemistry occurred simultaneously, allowing for frequent blood sampling to assess various biochemical and haematological parameters on much smaller blood volumes, and providing effective equipment for the monitoring of cardiorespiratory status. With the recognition of the importance of surfactant deficiency in hyaline membrane disease, many neonatologists moved towards a more active therapeutic approach with regard to oxygen therapy. Arterial pO2 could be measured by means of an indwelling umbilical artery catheter and it was realised that pO2 in most infants with hyaline membrane disease was well below normal adult levels.

The establishment of prolonged endotracheal intubation with polyvinyl chloride tubes as an alternative to tracheostomy, beginning in the early 1960s, facilitated the introduction of mechanical ventilation. Once it was demonstrated that infant, with what would have been terminal hyaline membrane disease could be successfully ventilated (Delivoria-Papadopoulos and Swyer, 1964), enthusiasm for this mode of therapy grew rapidly. The development of appropriate and reliable mechanical ventilators ensured that prolonged ventilation was possible. Concomitantly, techniques for delivering total parenteral nutrition were developed and the modern neonatal intensive care unit (NICU) came into being.

As the number of units that developed into NICUs increased, another important development occurred in the form of the regionalisation of perinatal care. It was realised that NICUs were

most appropriately situated in certain of the larger hospitals and that babies who required such care would have to be transferred to these units. However, it soon became apparent that transporting infants to an NICU after birth resulted in significant disadvantages to the infant, often with an increase in morbidity and mortality. Thus arrangements were made to transfer infants in-utero when it was thought that they may require intensive care after birth resulting in the development of organised regional perinatal services (Hack *et al,* 1979).

Thus towards the end of the 1970s, NICUs had become widespread in most parts of the industrialised world and, with the advent of regionalisation and transport networks, even infants born far away from an NICU could be offered such care.

2.4 Advances in Care of VLBW Infants since the late 1970s

Once NICU facilities became widely available, progress in the care of VLBW infants occurred rapidly. Fujiwara *et al* (1980) pioneered the use of artificial surfactant therapy for premature infants with respiratory distress syndrome. Since then numerous clinical trials have demonstrated the efficacy of exogenous surfactant in improving lung compliance, decreasing the incidence of air leak complications and increasing survival (Soll *et al,* 1990; Avery and Merritt, 1991; Soll and McQueen, 1992). Artificial surfactant was either purified from animal lungs (natural surfactant) or wholly synthesised in the laboratory (synthetic surfactant). Once clinical trials had demonstrated its efficacy and sufficient artificial surfactant could be produced for general clinical use, artificial surfactant was licensed for use in many countries from about 1990 onwards and is now routine therapy for VLBW infants with respiratory

distress syndrome in most modern NICUs.

Patent ductus arteriosus is a frequent complication of VLBW infants, particularly those requiring mechanical ventilation. Pharmacological and surgical closure of the ductus arteriosus came into routine use so that prolonged patency is seldom allowed in such infants. Since the classic study of Papile *et al* (1978) on the incidence and evolution of intraventricular haemorrhage an enormous amount of research took place in order to understand the pathophysiology of this condition and to devise strategies for prevention. While specific preventive strategies for intraventricular haemorrhage, pharmacological or otherwise, remain controversial, a better understanding of the pathophysiology of this condition together with better overall neonatal care appeared to bring about a reduction in its incidence (Volpe, 1989a; Philip *et al,* 1989).

An understanding of the fluid changes after birth of VLBW infants and their fluid and electrolyte needs have resulted in refinements of fluid management Improved formulations and easier techniques of parenteral nutrition have been developed. The nutrition of the VLBW infant has been a major area of research over this period since, with the improvement of survival of these infants, it was recognised that some aspects of their long term morbidity may be on the basis of poor nutrition during the early weeks and months of life. A number of studies were carried out on newer milk formulas for VLBW infants which showed improved growth when compared with standard formulas and this resulted in the widespread introduction of infant formulas specially designed for VLBW infants, as well as fortifiers that could be added to expressed milk breast for VLBW infants (Gross 1983; Tyson *et al,* 1983; Cooper *et al,* 1984; Cooper *et al,* 1985).

While the continuous flow, time-cycled pressure-limited ventilators able to deliver intermittent mandatory ventilation have been the mainstays of neonatal ventilation since the 1960s, newer modes of ventilation have been introduced. Ventilators that are patient-triggered and those able to deliver high-frequency ventilation have been extensively investigated in recent years. While they do appear to have advantages over conventional ventilation in certain neonatal conditions, their place in the overall management of ventilated VLBW infants is perhaps still uncertain (McGettigan *et al,* 1998). Other more experimental modes of therapy for improving gas exchange such as nitric oxide, liquid ventilation and extracorporeal membrane oxygenation cannot yet be recommended for VLBW infants (McGettigan *et al,* 1998).

However, in spite of all the advances that have taken place, many problems still remain. While the incidence of PV-IVH has decreased, the incidence of its ischaemic counterpart, periventricular leukomalacia, which is less well understood, has not declined and remains a factor in most VLBW infants who have long term neurological handicap (Perlman, 1996). Chronic lung disease remains as one of the major sequelae in ventilated VLBW infants in spite of the refinements in ventilator techniques and the introduction of artificial surfactant and is one of the consequences of keeping smaller and more immature infants alive (McColley, 1998). Of even greater concern has been the emergence of a 'new' epidemic of ROP, mainly confined now to extremely low birthweight infants born at less than 28 weeks of gestation. By the end of the 1970s, Phelps (1981) estimated that the number of infants blinded by ROP was similar to that of the 'epidemic' years of 1943 to 1953. This led to the realisation that the aetiology of this condition is far more complex than was previously appreciated and that oxygen therapy was only one of the components involved.

2.5 Modern Day Intensive Care and Mortality of VLBW Infants

The widespread introduction of modern day intensive care has resulted in substantial reductions in the mortality of VLBW infants. Although Jones *et al* (1979) were unable to show a significant improvement in the neonatal mortality of VLBW infants over three 5-year periods between 1961 and 1975 at a single institution in Britain, combined data from a number of institutions clearly demonstrated that survival of VLBW infants improved as a result of the introduction of modern day neonatal intensive care. Philip *et al* (1981) combined outcome data from several centres in England and North America from the 1960s until the late 1970s and showed that there was a progressive improvement in survival figures for VLBW infants over this time period. For infants with birthweight less than 1000g, survival had improved from 19% to 42%, for those 1000-1500g survival had improved from 56% to 82% and, for all VLBW infants combined survival had improved from 38% to 69%. The figures from their own institution in Vermont, United States, showed a remarkable similarity to the combined figures. The improvement in the survival figures from this analysis of the combined data is illustrated graphically in Figure 2.1.

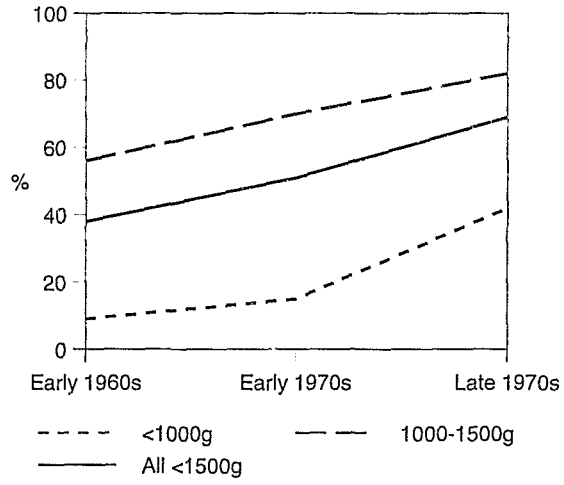


Figure 2.1 **Improvement in survival (%) of VLBW infants in selected centres in England and North America between the early 1960s and the late 1970s** (derived from Philip *et al,* 1981)

One of the centres included in the above combined analysis was the University of Colorado in the United States. Comprehensive neonatal mortality data for infants delivered between 1958 and 1969 at the University of Colorado Health Sciences Center in Denver were published by Lubchenco *et al* (1972) who analysed mortality both by birthweight and gestation. Subsequently Koops *et al* (1982) performed a similar analysis on infants born between 1974 and 1980 at the same institution. Outcome for VLBW infants was similar to the combined data collated by Philip *et al* (1981) as presented above with 84% of infants with birthweight 1000-1500g surviving in the latter period and 43% of infants less than 1000g surviving. The Colorado group showed that, whereas in the earlier time period a 50% mortality was found in the group 1000g/30weeks at birth, the 50% mortality figure had shifted to the 750g/26weeks group during the later time period. It is useful to review the major changes that had occurred

in Denver over this time period as described by the authors:

1. The routine provision of mechanical ventilation and continuous positive airway pressure for those infants who required it.
2. The presence in the delivery room of obstetrician, neonatologist and highly skilled nurses for the management of deliveries involving VLBW infants.
3. The encouragement of a positive attitude towards extremely premature infants amongst physicians, nurses, students and parents.
4. Continuously improving intrapartum monitoring and postnatal supportive care over the time periods studied.

The authors were of the opinion that these changes were common to most perinatal medicine centres in the United States and were largely responsible for the improvement in outcome, particularly for VLBW infants. It is possible too that, particularly in the early days of NICUs, extremely premature infants who may previously have been regarded as spontaneous abortions, were now counted as neonatal statistics. This makes these improvements in survival, especially for those less than 1000g at birth, even more impressive.

Further confirmation of the improvement in the survival of VLBW infants came from analysis of national data in the United States. Kleinman *et al* (1991) analysed data of singleton white infants born in the United States between 1960 and 1983 and showed an increase in survival for those weighing 500-999g from 7% to 46% and an increase from 42% to 85% for those weighing 1000-1499g at birth. Pharoah and Alberman (1988) analysed data from the United Kingdom and showed similar survival figures for England and Scotland by the mid-1980s.

The dramatic improvement in survival of VLBW infants has also been one of the major factors in the reduction in infant mortality in developed countries such as the United States over the past three decades. McCormick (1985) discussed this in relation to the decline in infant mortality that had occurred in the United States over the 15-year period from 1965 to 1980. During this time there was a 47% decrease in infant mortality in the United States and, unlike the decline in infant mortality in the first half of the century, this decrease was primarily a result of a reduction in neonatal mortality. Reviewing the cumulative data on the improvements in survival of VLBW infants since the introduction of NICUs and noting the facts that there had been only moderate decreases in the proportion of low birthweight infants, she concluded that "the accumulating evidence indicates that a major factor in the overall rapid decline (in infant mortality) has been the increased survival of low birthweight infants, in part as the result of more intensive, hospital-based management". This was supported further by a study conducted by Williams and Chen (1982) who analysed the sources of the decline in perinatal mortality rates in California over approximately the same time period. From 1960 to 1977 there was a decrease in the overall perinatal mortality rate of 11.6 per thousand in California of which only 2.2 per thousand could be attributed to an overall improvement in the birthweight distribution of the population, with weight-specific declines accounting for the remainder. The decline in the neonatal mortality rate was almost double that of the stillbirth rate and the greatest contribution to the reduction in overall mortality, especially neonatal, came from the improved survival of low birthweight infants.

The improvement in survival of VLBW infants since the early 1980s has continued to be impressive and the frontiers for survival at the lower extremes of birthweight and gestation continue to be pushed further and further back. As discussed previously, a major impetus to

improved survival of VLBW infants came about with the widespread introduction of artificial surfactant. Two products of artificial surfactant were introduced into general use in the United States in the last quarter of 1989 and Schwartz *et al* (1994) analysed the effect on United States national data. The chance of death in hospital for VLBW infants was reduced by 30% after surfactant was introduced and they estimated that 80% of the decline in the national infant mortality rate between 1989 and 1990 could be attributed solely to the use of surfactant. Thus the introduction of artificial surfactant, as with mechanical ventilation and other NICU techniques previously, not only had a major impact on survival of VLBW infants but had a substantial effect on overall infant mortality.

As the threshold for extra-uterine viability has been progressively lowered, numerous papers have been published questioning whether limits can be set and, if so, where. A study by Allen *et al* (1993) suggested that, on the basis of their outcome data, aggressive resuscitation was indicated for infants born at 25 weeks gestation and above, but not for those born at 22 weeks gestation or less. Those born at 23 or 24 weeks gestation represented a group with very high mortality and morbidity, but the conclusions from their study were that individual decisions needed to be made for these infants. However, as shown by Ferrara *et al* (1994), surfactant therapy has improved survival for all infants less than 26 weeks gestation and there is no agreement on whether limits should be set. Indeed intact survivors with birthweight less than 500g continue to be reported (Sauve *et al*, 1998).

In recent years, the most impressive survival figures for VLBW infants in general and those less than 1000g at birth in particular appear to have been reported from Japan. With its relatively homogenous population, the very high utilisation of antenatal services resulting in

optimal perinatal care and its well organised network of NICUs, the most recent survival figures indicated that, over the period 1989 and 1993, more than 30% of infants with a birthweight less than 600g survived (Oishi *et al*, 1997). On the basis of these data, they suggested a viability limit of 22 weeks gestation was appropriate for Japan.

2.6 The Effects on Morbidity of VLBW Infants

As has been the case with survival of VLBW infants, long term outcome with respect to disability and handicap has also been the subject of intense research over a number of decades. During the first half of this century when the pioneering work of Budin as described before was applied more generally, long term outcome for surviving VLBW infants was generally good. However, during the middle decades of the century when a number of practices led to iatrogenic complications, follow-up studies suggested that the rate of disability was high. Drillien (1964) reported that up to 60% of low birthweight infants followed to the age of five years in Scotland had deficits in mental and physical development, while Lubchenco *et al* (1963b) in the United States found similarly poor outcomes. Subsequently, with the advent of modern day neonatal intensive care, it appeared that the long term outlook for VLBW infants was improving and Hack *et al* (1979) reported that "most current follow-up studies demonstrate that accompanying the improved survival there is a decreased incidence of long-term sequelae, as compared with results reported before the new perinatal focus".

The references quoted by Hack *et al* (1979) in support of a decreasing handicap rate were, however, related to data from single centre studies. Other studies reviewed data from regional

catchment areas. For the example the study of Saigal *et al* (1989) reported a significant decrease in overall functional disability at age three years in infants weighing 800g to 1000g at birth between 1977 and 1984 concomitant with an improvement in survival, although the incidence of cerebral palsy in survivors did not decrease significantly (15% to 12%). Other reports, however, have suggested an increasing incidence of cerebral palsy in VLBW survivors. Kitchen *et al* (1987) reported a significant increase in cerebral palsy in VLBW survivors at the age of two years: 2.4% in the time period 1966 to 1970 compared with 12.5% in 1977 to 1982. Pharoah *et al* (1990) reviewed trends in cerebral palsy in the Mersey region in England between 1967 and 1984 and showed that, while the survival rate of VLBW increased from just under 40% to just over 70%, there was a five- to sixfold increase in the incidence of cerebral palsy when expressed per 1000 live births less than 1500g, suggesting that there was an increasing proportion of VLBW infants surviving with cerebral palsy.

With these conflicting reports, it was left to meta-analyses to attempt to unravel the true trends that have occurred with respect to handicap in VLBW infants. Escobar *et al* (1991) performed a meta-analysis on the outcome of surviving VLBW infants based on studies published over three decades. All studies published in an English language medical journal before March 1988 that reported on the outcome of infants weighing less than 1500g at birth and born after 31 December 1959 were included in their analysis. Studies that excluded infants in a non-random fashion, those that did not provide adequate data on the total number of infants enrolled in the follow-up study or failed to indicate those lost to follow-up and those that did not indicate the age at which outcomes were assessed were excluded from the final analysis. A total of 111 studies was included in the analysis, all from developed countries. The median incidence of cerebral palsy among all cohorts studied was 7.7% (CI 5.5 to 9.0), but there was

no improvement in the incidence with time. In fact the incidence of cerebral palsy in studies which enrolled infants after 1977 had a median of 8% versus 6% in the earlier period, but this difference was not significant. However, when they analysed the data to include all forms of disability, there was an improvement over time: when the midpoint of enrollment was between 1960 and 1977, the median rate of disability was 29.8% whereas, when the midpoint was between 1978 and 1986, the median rate was 21.4% (p=0.04). Paneth *et al* (1981) estimated the rate of cerebral palsy in surviving VLBW infants at 8.1%, very similar to the rate found in the meta-analysis by Escobar and, in a subsequent review of the literature, Bhushan et al (1993) concurred with the Escobar study that there was no convincing evidence that there was any significant decrease in the rate of cerebral palsy in VLBW survivors over time.

In summary, it is apparent that the question as to whether the incidence of handicap in infants of very low birthweight has increased over the past five decades is a complex one. As indicated by McCormick (1993) in a review of this question, the brief answer could be "probably yes, although not necessarily"! There is some evidence to suggest that there may have been periods during the past 50 years when the rates of handicap did increase. For example, as previously discussed, during the 1950s when the association between oxygen therapy and ROP was reported and oxygen therapy was restricted, neonatal deaths and neurological handicap among survivors increased . The widespread application of neonatal intensive care techniques between the mid 1960s and the mid 1970s in many developed countries may also have resulted in a temporary increase in handicap as the caregivers went through the 'learning curve' associated with their introduction, while the dramatic increase in survival of infants less than 750g in recent years in some countries has not yet been fully evaluated as regards the effects on later morbidity. However, there is no convincing evidence

from the literature that there has been a significant trend towards either an increase or a decrease in the proportion of surviving VLBW infants who have cerebral palsy and it is probable therefore that the rates have remained more or less the same. In a more recent review addressing the post surfactant era, Bregman (1998) reached a similar conclusion, namely that the increased survival of VLBW infants as a result of surfactant treatment had not resulted in any change in long term morbidity. However, as in the past, the chance of intact survival at the edge of viability is very poor. Allen *et al* (1993) suggested that over 60% of survivors born at less than 25 weeks gestation would have major neurodevelopmental handicap and/or severe visual deficits, while Hack *et al* (1994) reported that, for infants less than 750g at birth, the rates of neurobehavioural dysfunction and poor school performance were high, even in infants who did not have major neurological handicaps.

2.7 Conclusions

The 20th century has seen enormous advances in the care of VLBW infants that are equal to those in any other field of medicine. However, in the face of a marked decline in mortality of VLBW infants over many decades it appears that the rate of cerebral palsy and other forms of handicap in VLBW survivors has remained constant. From these data a number of important implications follow:

1. ***Those infants currently surviving with handicap probably have perinatal complications that would have resulted in death in previous years, while those who would have survived with handicap in the past are probably now surviving intact or***

with only minor disabilities. Thus the entire spectrum of survival without handicap, survival with handicap and death appears to have shifted.

2. *The absolute number of infants entering the community with significant handicap has increased given the fact that survival has increased but the proportion of handicapped survivors has remained the same. This has major implications for the services responsible for the management of children with handicap, since there is an increased demand for such services.*

3. *The absolute number of infants surviving intact, however, shows the greatest increase and this is frequently and probably justifiably used to argue in favour of the provision of intensive care for VLBW infants.*

Chapter 3

VLBW Infants in South Africa

Preamble

The care of VLBW infants at Baragwanath Hospital since the opening of a neonatal unit in 1950 has broadly followed the advances in neonatal care that occurred in industrialised countries, albeit usually lagging some years behind and with many limitations due to the lack of resources. This chapter traces the development of the care of VLBW infants at Baragwanath Hospital over the past half century and describes some of the political and sociological factors that influenced the overall profile of infants seen in the neonatal unit at Baragwanath. Comparisons are made with public sector institutions in other centres in Southern Africa, caring largely for black infants as well as with institutions caring for white infants, both public and private.

Historically, neonatal care in South Africa, particularly as it related to VLBW infants, reflected the trends in the broader society. Public health facilities, divided along racial lines, were a feature of health care in the country. This resulted in markedly unequal standards of care in the public sector with the best standards of care generally being available for whites, intermediate standards available for Asians and those of mixed race, and the poorest available for blacks. In urban areas where larger hospitals often developed in association with academic institutions, facilities were generally better, but, in the more peripheral and rural areas, health care facilities were frequently rudimentary. On the other hand, over the past few decades health

facilities in the private sector, generally provided on a fee-for-service basis and utilised predominantly by whites in the past, developed along first world lines and provided services for only about 20% of the population (Makan *et al,* 1996).

The neonatal services developed at Baragwanath Hospital illustrate the changes in care that have taken place over the last 40-50 years for sick and premature infants in the largest black urban complex in South Africa. Soweto was developed on the outskirts of Johannesburg in the 1930s as a black urban residential area or township. Few health facilities were available until Baragwanath Hospital, which was first a military and then a tuberculosis hospital, was converted in the late 1940s to one that would serve the needs of the people of Soweto. The hospital also became a teaching hospital of the Medical School of the University of the Witwatersrand.

3.1 Neonatal Care at Baragwanath Hospital 1950-1982

A unit for the care of premature babies was established at Baragwanath Hospital in 1950. Kahn *et al* (1954) reported on the outcome of the first thousand consecutive admissions to the unit in the early years after it was established. Infants were nursed in an open ward heated by coal-stoves. No incubators were available and infants were placed in wooden box-like cots, wrapped in blankets and temperature maintenance was enhanced by the use of electrically heated pads. Oxygen was available for infants with respiratory distress or cyanosis. In keeping with the practices of that era, premature infants were not fed for the first 24-72 hours of life and, thereafter, feeds were administered by pipette. Tube feeding was not utilised and

techniques for providing intravenous fluids were not available. All mothers were kept in hospital for the duration of their infants' stay since most of the infant care was provided by the mothers under supervision of the nursing staff.

Approximately half of the infants were born at Baragwanath Hospital, while the remainder were born at home or in ambulances and the casualty departments of other hospitals. Infants born in the hospital and dying before they could be admitted to the unit were excluded from the report, while presumably many infants born outside the hospital died before they could be brought to hospital. The Baragwanath figures were thus biased towards counting those who had declared themselves as potential survivors. Nevertheless the results obtained were impressive and compared favourably with results from Sorrento Hospital in Birmingham, England at that time. Results were as follows:

Table 3.1 Survival of low birthweight infants at Baragwanath Hospital and Sorrento Hospital, Birmingham in the early 1950s (Kahn *et al,* 1954)

Birthweight (g)	Percent Survival	
	Baragwanath	Sorrento
<907g	2%	0%
907-1360g	25%	32%
1361-1813g	62%	74%
1814-2267g	82%	90%
2268-2494g	89%	97%

Note: The original publication gave the weight in pounds and these have been converted to grams (1 pound = 453.6g).

What was not appreciated at that time was that many low birthweight infants were growth retarded and that growth retardation was much more common where socioeconomic conditions were poor, especially in developing countries. Thus although the weight-specific mortality at Baragwanath Hospital was similar to that in Birmingham, it is probable that gestation-specific mortality was significantly worse. However, in the light of the simple techniques used and the lack of the more sophisticated equipment that was available at that time, these results were remarkable and this system served as a model that was subsequently used in many countries in the developing world (Stein, 1982).

After the publication by Dubowitz *et al* (1970) describing the clinical assessment of gestational age in term and premature infants, Stein and Ellis (1974) examined 250 low birthweight infants admitted to the premature baby unit at Baragwanath Hospital between November 1971 and June 1972. Due to the lack of reliable information regarding the dates of the last menstrual period, the assessment of gestation was based on the Dubowitz criteria. Their results showed that 73% of infants with birthweight less than 2500g were SGA when assessed on the intrauterine growth curves developed by Lubchenco *et al* (1963a). While there may be reservations regarding the accuracy of the Dubowitz score in the absence of some other measure of gestational age, there can be no doubt that the rate of growth retardation was extremely high. Stein and Ellis (1974) did not analyse their data separately for infants with birthweight less than 1500g, but, as shown in Figure 3.1, the birthweight/gestational age distribution showed a concentration of SGA infants weighing 1500-2000g and born between 35 and 38 weeks of gestation, while those less than 1500g at birth appeared to have a lower rate of growth retardation.

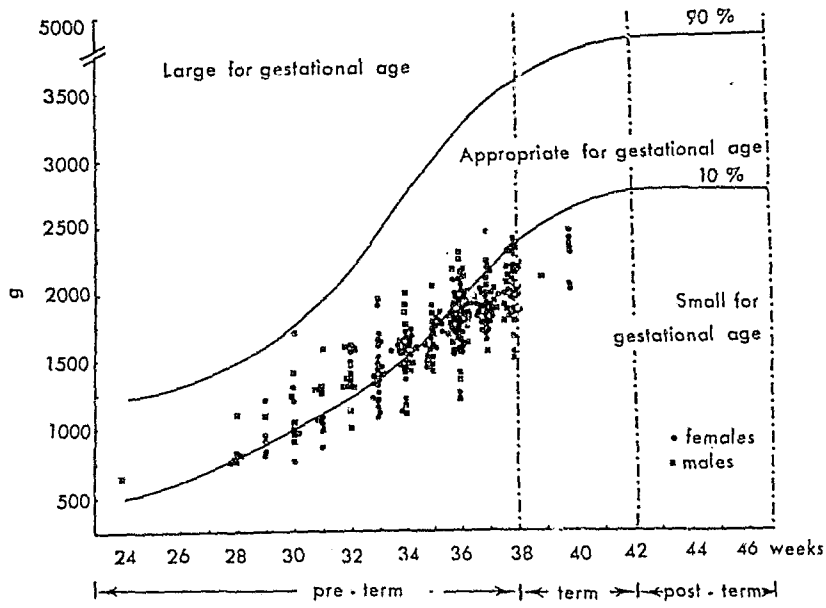


Figure 3.1 Low Birthweight Infants at Baragwanath Hospital Plotted by Weight and Gestation (from Stein and Ellis, 1974)

In a further study on mothers of low birthweight infants at Baragwanath Hospital, Stein (1975) demonstrated that maternal protein depletion due to chronic malnutrition correlated with the delivery of SGA infants, particularly when maternal serum albumin levels were below 30g/l.

It should be noted at this point that there has been much debate in the literature regarding what constitutes appropriate intrauterine growth. As described above, Stein and Ellis (1974) utilised the intrauterine growth curves derived by Lubchenco *et al* (1963). These curves have been criticised for a number of reasons, e.g. they were derived at a time when gestational age assessment was unreliable, few infants less than 28 weeks gestational age were included and

they were derived in Denver, Colorado in the United States which is situated at a considerable altitude (Keen and Pearse, 1985). Subsequent growth curves were derived at sea level by Usher and McLean (1969) in North America and numerous workers in other (mostly industrialised) countries, most of which showed better standards of intrauterine growth than that demonstrated by Lubchenco *et al* (1963). Dunn (1985) attempted to derive an international reference for perinatal growth, but his charts have not been widely applied. Since the study of Stein and Ellis (1974), hospitals in Johannesburg attached to the University of the Witwatersrand have used the Lubchenco charts since Johannesburg is at a similar altitude to Denver. It should therefore be noted that the Lubchenco charts have been used throughout the series of studies in this thesis. The author recognises the limitations of these charts and it is important to appreciate that infants classified as SGA by the Lubchenco norms are extremely growth retarded by most other international reference standards.

The apartheid policies of the South African government resulted in a stabilisation of the population of Soweto during the 1970s, since the main purpose of this policy was to halt the continuing influx of black people from the rural areas into the so-called white urban areas. A complex set of laws were enacted that made it extremely difficult for those not resident in urban areas to settle in these areas. However, those born in an urban area had a right to permanent residence in such an area and the easiest way to prove an 'urban' birth was for such a birth to take place within the public sector health care system which resulted in official registration of the birth. Primary health care clinics were established in Soweto in an attempt to provide appropriate primary health care for the population and, in the case of seven of these clinics, low risk deliveries took place under the supervision of nursing sisters. These clinics worked under well-defined protocols with automatic referral to Baragwanath Hospital should

the criteria for referrals be met. Thus a regional perinatal service for the whole of Soweto came into existence which, compared with a total of just over 5000 births in 1956, was responsible by the end of the 1970s for more than 25000 deliveries in a population that was estimated to be about 1.5 million (Stein, 1982). Due to the prevailing political policies whereby the registration of a birth of a baby in an urban area was extremely advantageous, the overwhelming majority of deliveries in Soweto took place either at the hospital or at one of the clinics, or the baby was brought to one of the facilities soon after birth. As a result, it was estimated that less than 1% of babies born within the greater Soweto area did not pass through the Baragwanath Hospital/Soweto Clinic complex at this time (Rissik, 1983).

The result of these developments was a marked improvement in the perinatal and infant mortality rates in Soweto. It was estimated that the low birthweight rate fell from 20% to less than 15% during the 1970s, at least in part due to improving maternal nutrition, while perinatal mortality fell from 90/1000 in 1965 to 47/1000 in 1978 (Stein, 1982). Infant mortality for blacks in the Johannesburg municipal area, which had been more than 200/1000 live births in 1950, fell from 81/1000 in 1970 to 35/1000 in 1979 (Medical Officer of Health, 1979). However, these figures were not typical of the country at large. Infant mortality rates for blacks living in 34 selected urban areas for which there were statistics available showed an infant mortality rate that improved from 124/1000 to 86/1000 between 1970 and 1980 (Herman and Wyndham, 1985), while the rate for rural Transkei was reported to be 130/1000 in 1980 (Irwig and Ingle, 1984).

The collection of birthweight related survival data at Baragwanath Hospital, however, had been patchy over this entire period due to the rapid increase in delivery numbers and a poor

infrastructure of record keeping. A new system of record keeping was introduced in 1979. This was developed under the supervision of a single individual, Dr Judy Rissik, and, although it was an extremely time consuming manual system, it proved to be very reliable in providing comprehensive statistics for the Baragwanath Hospital/Soweto Clinic perinatal service. By this time, major advances had taken place in the care of low birthweight infants compared with the era of the early 1950s as described by Kahn *et al* (1954). A new maternity hospital was opened in 1974 with several of wards for neonates who required special care. Prolonged starvation in the early neonatal period was no longer practised and intravenous fluids were routinely administered. Broad spectrum antibiotics were available, tube feeding was routinely practised in infants with gestation <34 weeks, infants were nursed in incubators until such time as they could maintain normal body temperature, and oxygen was administered in a far more controlled manner either via the incubator or with the use of a 'headbox'.

The marked reduction in infant mortality rate during the 1970s in Soweto resulted more from a decline in postneonatal mortality, although neonatal mortality also fell (Herman and Wyndham, 1985). As a result neonatal mortality constituted half of all infant deaths by the end of the decade and it was therefore considered appropriate to open an NICU. This took place in 1979 with provision for mechanical ventilation of up to six infants at a time. Due to the limitation of resources, infants less than 1000g at birth were not offered ventilation in the NICU, while even above this birthweight it was necessary to be selective as to who was admitted.

Using the new data collection system, Rissik reported a further reduction in perinatal mortality rate from 47/1000 in 1978 as reported by Stein (1982) to 38/1000 during the years 1981-1982

(Rissik, 1983). She also analysed mortality by birthweight during 1981-1982 according to 500g intervals for all VLBW infants born at Baragwanath Hospital. Those born outside of the hospital were excluded due to the unknown denominator. Although the NICU was opened in 1979 and significant numbers of VLBW infants were admitted, given the fact that there were only six NICU beds for a delivery service that had reached almost 30000 at this time, it was probable that the full impact of an NICU on the mortality of VLBW infants had not yet been effected, even for those over 1000g at birth. It should also be recognised that, in the case of infants less than 1000g at birth, many who may have shown signs of life but died soon after birth may have been classified as abortions because the parents could not afford the cost of a funeral. They were thus not included in neonatal statistics. This continues to affect statistics even at the present time.

At this time, Johannesburg Hospital was allowed to admit only white infants. The NICU at that hospital, although comparable in size to that of Baragwanath, had a far smaller population base to serve and was therefore able to ventilate infants less than 1000g at birth. In addition, the NICU had more experienced nursing staff since the unit had been ventilating infants for more than ten years and had a better staff to patient ratio. Birthweight specific mortality for infants less than 2000g at birth who were admitted to the neonatal units of both hospitals can be seen in Table 3.2.

Table 3.2 **Birthweight specific mortality for infants with birthweight <2000g born at Baragwanath Hospital during 1981-1982 and Johannesburg Hospital 1983** (Rissik, 1983; Davies *et al,* 1985)

	Survival	
Birthweight	**Baragwanath**	**Johannesburg**
<1000g	13.9%	43.8%
1000-1499g	63.6%	82.4%
1500-1999g	91.5%	93.8%

Analysis of the above figures for Baragwanath Hospital shows that, although the weight groups were not strictly comparable with the study reported by Kahn *et al* (1954) 30 years earlier due to the use of pounds and ounces in the earlier study and differing criteria for inclusion in the analysis, there was clearly a marked improvement in survival of low birthweight infants at Baragwanath Hospital. For example the survival figure in the early 1980s of infants 1000-1499g was similar to that of infants 1359-1812g (3-4lbs) in the early 1950s and it is probable, in the light of the description above, that much of this improvement had been brought about prior to the introduction of mechanical ventilators. On the other hand, when compared with outcome figures for white infants at Johannesburg Hospital, the survival of VLBW infants at Baragwanath Hospital was clearly much worse. In comparison with the survival figures compiled by Philip *et al* (1981) who combined outcome data from several centres in England and North America as illustrated earlier in Chapter 2, the Baragwanath figures were similar to Philip's data from the early 1960s prior to the introduction of neonatal intensive care in developed countries, while those for Johannesburg Hospital were similar to Philip's data from the late 1970s when neonatal intensive care was already widely practised in those countries.

3.2 Development of Neonatal Services Elsewhere in South Africa

Neonatal units developed in association with maternity services in most parts of South Africa, but as described previously, the quality of these units varied greatly, often depending on whether they were attached to academic centres.

Tertiary hospitals attached to academic centres developed the first neonatal intensive care units in the 1960s and indeed one of the earliest reports in the literature on assisted ventilation originated from Cape Town (Heese *et al*, 1963). Over the next two decades, such units developed in all of the tertiary academic institutions. In addition a small number of regional hospitals also developed neonatal intensive care units. Aiding this process was the fact that several South African neonatologists trained in countries such as the United States and, with the help of ongoing scientific exchanges, were able to introduce many of the innovations in neonatal intensive care along the lines of those discussed in Chapter 2. However, the NICUs that developed in the public sector hospitals were usually unable to provide intensive care for all neonates requiring such care. Facilities were not even able to cope in many areas with all of the white infants who required intensive care. In a study covering the period 1983-1984, Cooper *et al* (1987) surveyed Johannesburg and surrounding metropolitan areas and showed that only half of the calculated neonatal intensive care beds that were required were available for white infants. At that time, private hospitals were just starting to develop neonatal intensive care facilities, but the majority of infants covered by medical insurance were still being ventilated in public sector institutions. Subsequently, as a result of the government's inability to finance an expansion of public sector facilities and its stated policy at that time of encouraging the growth of private sector facilities, NICUs in the private sector experienced

a rapid increase in size and number. The situation for other population groups, especially blacks, as regards neonatal high care facilities in the Joahnnesburg area in 1983-1984 was much worse (Cooper *et al,* 1987).

At the other end of the spectrum, infants born in public sector facilities in large parts of the country or born outside of health care facilities have historically had virtually no access to intensive care facilities. Thus the situation in recent years has been that those with access to private health care have largely been able to make use of the full range of neonatal facilities, those born in tertiary public sector hospitals and certain regional hospitals with their own intensive care units or able to refer infants to tertiary hospitals have had access to a full range of neonatal facilities but with a significant degree of rationing on the basis of specific admission criteria, e.g. birthweight greater than 1000g, availability of intensive care facilities, etc., while those outside of these referral systems, have had virtually no access to neonatal tertiary or intensive care.

Birthweight specific mortality data in South Africa was not generally available. However, the annual Conferences on Priorities in Perinatal Care in South Africa began in 1982 and were attended by neonatologists, obstetricians, epidemiologists, health educators and others involved in perinatal health care. The conferences aimed to provide a forum for the presentation of research data from different regions of the country and served as a stimulus for those involved in the care of low birthweight infants to analyse their local and regional outcome data. While most of these data were hospital-based, they were derived mainly from academic tertiary institutions similar to Baragwanath Hospital which served large regional populations and acted as the referral centre for all low birthweight infants in the region. These

data, however, were invariably from urban and peri-urban areas and accurate data from the more rural parts of the country were extremely difficult to obtain. In rural areas many deliveries occurred at home at great distances from hospitals or clinics and sick, premature infants often died long before transfer to a neonatal unit could be organised.

3.3 Data from the Conferences on Priorities in Perinatal Care

Data on the survival of low birthweight infants between 1980 and 1983 were reported from most of the larger urban centres of South Africa during the first few Priorities Conferences. There was, however, some variation in the reporting of the data. The data from Cape Town (Malan *et al,* 1983) included stillbirths and were thus weight-specific perinatal figures, while the data from East London (Power and Bok, 1983), Garankuwa (Hay *et al,* 1983) and Bloemfontein (Wessels *et al,* 1984) included early neonatal deaths only. Data were also presented from Harare, Zimbabwe (Whaley, 1984). With the exception of the units in Cape Town and Tygerberg (Henning and Beyers, 1984) which cared mainly for infants of mixed race who form the majority of the population in that part of the country (Western Cape), all of the reported data were on black infants. Most of the neonatal units at that time were able to offer mechanical ventilation, but facilities were usually limited and, with the exception of units in Cape Town and Tygerberg in the Western Cape which historically received better per capita funding for health care than the rest of the country, and some units in largely white hospitals, infants with a birthweight less than 1000g were seldom ventilated and ventilation was offered selectively even above this birthweight. Paediatricians and obstetricians in the Western Cape also took the initiative to regionalise services long before this happened

elsewhere in South Africa. As mentioned above, people of mixed race form the majority in that part of the country and historically they occupied an intermediate position in terms of socioeconomic status between whites and blacks, and health statistics such as perinatal and infant mortality rates were also intermediate.

A summary of the survival of low birthweight infants as reported at the Conferences in Perinatal Priorities covering infants born in the years 1980 to 1983 can be seen in Table 3.3.

Table 3.3 Survival of low birthweight infants in South Africa 1980 to 1983

Region	Author	Year Surveyed	Survival (%) by Birthweight Category		
			<1000g	1000-1499g	1500-1999g
Cape Town	Malan	1983	33.6%	84.1%	
Tygerberg	Henning	1983	27.2%	72.2%	95.2%
Durban	Adhikari	1980	10.0%	48.0%	89.0%
Garankuwa	Hay	1983	11.4%	63.2%	86.4%
Bloemfontein	Wessels	1983	12.0%	52.0%	
East London	Power	1981-1982	15.6%	73.5%	91.8%
Harare	Whaley	1983	22.0%	57.7%	87.8%

References: Malan *et al* (1983); Henning and Beyers (1984); Adhikari (1983); Hay *et al* (1983); Wessels *et al* (1984); Power and Bok (1983); Whaley (1984).

It can be seen from Table 3.3 that, where socioeconomic conditions were better and perinatal services were regionalised as was the case in the Western Cape and as shown earlier for white infants in Johannesburg, neonatal outcome of VLBW infants was better. In fact the survival figures for VLBW infants in Cape Town were remarkably good, being similar to the

Johannesburg white figures and approached those reported in developed countries at that time. In those institutions serving black populations, outcome figures were substantially worse and the average survival for the four South African centres listed in Table 3.3 was 12.3% for infants less than 1000g birthweight and 59.2% for those 1000-1499g at birth, only marginally worse than the 13.9% and 63.6% survival reported by Rissik (1983) for Soweto in 1981-1982. The figures for Harare, Zimbabwe, were also comparable.

Thus by the early 1980s, neonatal survival figures of VLBW infants in Soweto and other black urban and peri-urban areas in Southern Africa with limited NICU facilities were broadly similar to that of developed Western countries approximately 20 years earlier prior to the widespread introduction of neonatal intensive care.

3.4 Neonatal Care at Baragwanath Hospital after 1982

During the 1980s, the NICU at Baragwanath Hospital continued to expand until it reached its present capacity of 12 intensive care cribs able to provide mechanical ventilation. However, the policy of not ventilating infants with birthweight less than 1000g which was introduced at the time of opening the intensive care unit in 1979 did not change since, with the increase in numbers of VLBW infants, it was found that the NICU was invariably full even without infants less than 1000g. Indeed, it was practice at this time to set up additional ventilators in the high care area to ventilate infants (>1000g) who required ventilatory support when the intensive care unit was full. This area, however, was not staffed for this level of care and the results of attempts to ventilate infants out of the confines of the NICU were sometimes sub-

optimal. Nevertheless, it was felt to be a viable option, since it was seldom that an available NICU bed could be found at one of the other hospitals in the region.

Political changes continued to result in major socio-demographic changes with significant effects on the profile of the neonatal population at Baragwanath Hospital. In the early 1980s, political reforms did away with the 'influx control' laws which strictly controlled the movement of black people from the rural areas into the urban areas. This resulted in a massive migration of people from the rural areas resulting in informal settlements or 'squatter areas' developing very rapidly both in Soweto and in the areas adjacent to Soweto. Since none of these areas had health care facilities at that time, the Baragwanath Hospital/Soweto Clinic facilities were utilised. Although accurate data were not available, the fertility rate of resident Soweto women had been declining in association with the improvement in perinatal and infant mortality rates (Prof C. J. Van Gelderen, personal communication). However, the fall in fertility rate was matched by the rapid migration of people from the rural areas with the result that delivery numbers in the Baragwanath Hospital/Soweto Clinic complex continued to increase and by 1990 a total of 36000 deliveries took place. In addition, a small but increasing number of women were covered by medical insurance and were therefore able to utilise private hospitals. This latter group of women would be expected to have the best perinatal risk profile, while those recently arrived from rural areas and living in informal settlements would be expected to have the worst risk profile. Thus the socioeconomic status of women utilising the perinatal services declined while the perinatal risk profile worsened comparatively during the 1980s and this was further aggravated by a static or negative growth in Gross National Product and declining health budgets from the mid-1980s onwards.

Unfortunately, the system of data collection started by Rissik was largely dependent on the individual and, when she left the unit, the system no longer continued to function effectively. This author had been working as a neonatologist at Johannesburg Hospital until he moved to the neonatal unit at Baragwanath Hospital in June 1988. Having assisted in setting up a computerised neonatal database for the neonatal unit at Johannesburg Hospital, it was clear that, in order to collect adequate neonatal statistics, a similar database needed to be set up for the neonatal unit at Baragwanath Hospital. Working with Dr Steven Wainer, a neonatal database was established utilising a personal computer and the D Base III program (subsequently converted to D Base IV).

While this database was being established and preliminary data were becoming available, an interesting comparative study was done in the Johannesburg area utilising neonatal statistics from three hospitals during 1989.

3.5 Comparative Data from Three Johannesburg Hospitals

Wainer and de Ravel (1991) compared perinatal statistics for Baragwanath Hospital which served an urban black population, Johannesburg Hospital which served a predominantly white population in a public sector facility and the Park Lane Clinic, one of the largest private hospitals in Johannesburg serving a predominantly affluent white population with a fully developed NICU. The comparative perinatal and neonatal (deaths in the first 28 days) mortality rates per thousand deliveries can be seen in Table 3.4.

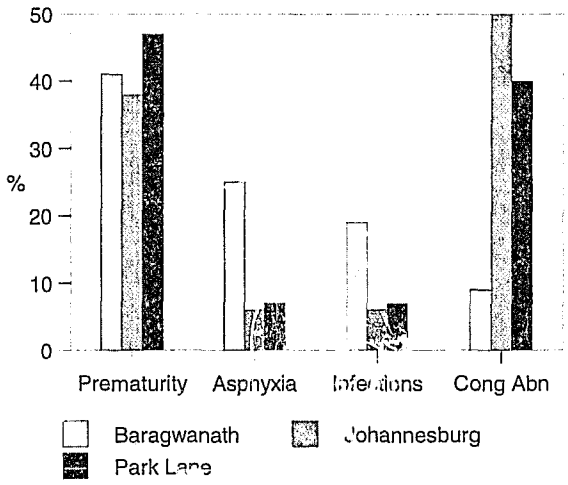
Table 3.4 Low birthweight, perinatal and neonatal mortality rates at three Johannesburg hospitals (Wainer and de Ravel, 1991)

	Baragwanath	Johannesburg	Park Lane
Low birthweight (%)	15.7	12.2	9.5
PNM rate / 1000	37.2	18.1	8.1
NNM rate / 1000	16.7	8.1	3.7

PNM - Perinatal Mortality
NNM - Neonatal Mortality

It can be seen that Baragwanath had the highest rates for low birthweight and mortality, Johannesburg had intermediate rates while the Park Lane had the most favourable. In fact, mortality rates at Baragwanath were double that of Johannesburg Hospital and more than four times higher than the Park Lane Clinic. The poorer outcome for Johannesburg Hospital compared with the Park Lane, both serving predominantly white populations at that time, could be explained by the fact that the former was dealing with a more indigent population and also acted largely as a referral hospital for complicated deliveries in the region, a number of which were referred from the private sector.

Of further interest was the comparison of cause specific neonatal mortality as can be seen in Figure 3.2. Both Johannesburg Hospital and the Park Lane had a 'first world' pattern of neonatal mortality with prematurity related causes (respiratory distress syndrome, intraventricular haemorrhage, extreme prematurity etc.) and congenital abnormalities together making up close to 90% of the deaths in roughly equal proportions. By contrast, deaths related to birth asphyxia and infection, both congenital and acquired, made up a far larger proportion of neonatal deaths at Baragwanath, but the proportion of deaths due to prematurity was the same as for the other two hospitals. Since deaths related to prematurity occur mainly in VLBW infants, the comparative 'load' of VLBW infants on the neonatal services at the three institutions that were very different in patient profile was remarkably similar.



Note: A small number of miscellaneous causes of death are not reflected in the figure.

Figure 3.2 Comparison of the causes of neonatal mortality at three Johannesburg hospitals

3.6 The Baragwanath Computerised Neonatal Database

Data entry into the computerised database was commenced in October 1988, but due to the large numbers of infants requiring admission to the neonatal wards, was initially limited to those admitted to the NICU (approximately 550 annually). It was only in October 1989 that it became logistically possible to expand the database into a comprehensive one into which all of the approximately 3000 annual neonatal admissions could be entered. The information entered included basic demographic data such as maternal age, area of residence and the number of previous pregnancies; obstetric information such as pregnancy complications and mode of delivery; the status of the infant at birth including Apgar score, birthweight and gestation; and information regarding all of the clinical complications experienced by the infant. This was divided into systems such as respiratory, cardiac, central nervous system, infections, etc., and, for those infants admitted to the NICU, details regarding their needs for mechanical

ventilation and course on the ventilator were recorded. The eventual outcome of the infant was also entered and, in the case of death, the cause of death as well. Most of the information was entered according to predetermined codes whereby the common conditions were all coded on the data collection form, but, in addition, there was space for information that could be entered as free text.

The neonatal bedletter was adapted so that the first two pages contained the data that was to be entered onto the computer, while in the case of admissions to the NICU, a separate more detailed data entry sheet was utilised. Samples of these data entry forms can be seen in the Appendices 1 and 2. In the case of NICU admissions, data entry took place at the time of discharge from the NICU or death while the bedletters of all infants were sent for computer entry at the time of hospital discharge or death. The first year of complete data on all neonatal admissions was 1990.

3.7 Changes in the 1990s

The year 1990 also corresponded with major changes that were taking place politically in South Africa. After the release of a number of political prisoners in 1989, the South African Government released Mr Nelson Mandela in February 1990 and, recognising that major political changes were inevitable, desegregated the health services in that year. Until this time, black people living in the central areas of Johannesburg and in the (historically) white suburbs, usually as domestic workers, were required to utilise Baragwanath Hospital for maternal and neonatal care. This changed entirely after 1990 and those living in Johannesburg soon began to utilise hospitals closer to their place of abode, in particular Johannesburg Hospital. It is also probable that the trends noted during the 1980s of a falling fertility rate and increasing utilisation of private medical care continued. However, accurate data on these trends could not be obtained.

The result of these changes was a significant decrease in delivery numbers at Baragwanath Hospital which in turn resulted in less pressure on the NICU and high care beds although, as

will be shown, the drop in the numbers of VLBW infants was far lower. This resulted in better all round perinatal care within the hospital and, in particular, more individualised care for VLBW and extremely sick infants. Artificial surfactant became available in South Africa in late 1991, but its use was limited somewhat by the high cost of the product and the consequent need to use the product more selectively than was the case in developed countries and in the private health sector of South Africa. Another major factor to affect the overall perinatal care of women and neonates in South Africa was the introduction of free health care for pregnant women and children under the age of six in June 1994. This was one of the first initiatives of the new government after the first democratic election in South Africa in April 1994. The result of this new policy was that the average period of gestation of first attendance at antenatal clinic fell from 28 to 23 weeks and the number of women delivering without attending antenatal clinic fell from 15% to 5% (Dr J.A. McIntyre, personal communication).

3.8 Conclusions

Solid foundations for the appropriate care of VLBW at Baragwanath Hospitals were laid by Kahn and others almost 50 years ago. The results they obtained with limited resources were most impressive and, in spite of an enormous increase in the size of the perinatal service over the next 40 years, major advances continued to take place resulting in significant improvements in the survival of these infants, comparable and sometimes better than that occurring in other parts of the country. However, the socio-political climate ensured that resources for the neonatal unit were always limited and the profile of VLBW infants differed from that typically seen in developed countries. Furthermore, record keeping over this period was seldom good and long term outcome data for VLBW infants were non-existent.

Chapter 4

Research Questions on VLBW Infants at Baragwanath Hospital

Preamble

On the author's arrival at Baragwanath Hospital in mid 1988, a number of research questions presented themselves regarding VLBW infants. These ranged from the fact that there were no birthweight specific survival data since the early 1980s, the profile of respiratory distress syndrome and intraventricular haemorrhage in VLBW infants at Baragwanath Hospital had not been adequately studied and the possibility that outcome of infants with birthweight <1000g may be improved by simple interventions other than mechanical ventilation, to the extremely important question regarding the long term outcome of surviving VLBW infants.

4.1 Survival of VLBW Infants

Since the detailed analysis of the Baragwanath statistics by Rissik (1983) in the early 1980s, significant changes had occurred both in the neonatal unit and in the socio-demographic profile of the population using the perinatal services.

The NICU had expanded from being able to ventilate only six infants at a time to a capacity of 12. Furthermore, the first few years after the intensive care opened in mid-1979 could be regarded as representing a 'learning curve' for the staff involved in the care of these infants.

Although a few of the nursing staff at the time of the opening of the unit had previously received training and practical experience in the Main Intensive Care Unit at Baragwanath Hospital which cares for older children and adults, none had any experience or formal training in neonatal intensive care. It was also the practice of the nursing administrators to rotate staff frequently between the NICU, the low care neonatal wards, the labour ward and the obstetric ante- and postnatal wards, since 'overspecialisation' in one area was regarded as detrimental to the long term career paths of the nursing staff. No general recommendations existed in South Africa for the ratio of nursing staff to infants in an NICU. At that time the NICU at Johannesburg Hospital had a ratio of one nursing sister to two infants on ventilators, but the NICU at Baragwanath Hospital had a ratio that was usually 1:3 due to the fact that the increase in bed numbers had been 'unofficial' and had not therefore been accompanied by an increase in nursing staff. Nevertheless, by 1988, the NICU at Baragwanath Hospital had achieved a degree of stability in terms of a core of experienced nursing staff, was reasonably equipped by South African standards and functioned largely according to a set of accepted protocols.

On the other hand, as indicated above, the socio-demographic changes that occurred in the greater Soweto area had resulted in the rapid growth of many informal settlements ('squatter areas') which utilised the perinatal services provided by the Soweto Clinics and Baragwanath Hospital, while the small emerging middle class was beginning to utilise the private sector facilities in increasing numbers. Thus, the risk profile of the population utilising the public sector facilities was thought to be worsening as indicated in Chapter 3.

In the light of these trends, i.e. an expanding and more experienced high care facility in the face of an increasing risk profile of the perinatal population, the effects on the survival of

VLBW infants needed to be fully assessed.

4.2 The Incidence of Respiratory Distress Syndrome

It had generally been accepted, both in Johannesburg and in South Africa, that the incidence of respiratory distress syndrome (RDS) due to surfactant deficiency in premature newborn infants appeared to show ethnic differences, being more common in white infants and less common in black infants and those of mixed race. Previously reported figures from Cape Town showed a lower incidence in black and mixed race infants compared with white infants, although most of the data from the Cape Town area related to infants of mixed race and there were few black infants in those studies (Malan *et al,* 1974; Rush and Segall, 1978). There had been no local studies on the incidence of RDS in significant numbers of black VLBW infants. Data from the United States also showed a difference in the incidence of RDS between black and white infants (Gluck, 1979; Collaborative Group on Antenatal Steroids, 1981). In addition, there was evidence from a study by Olowe and Akinkugbe (1978) that the surge in the production of lecithin, which is the major constituent of surfactant, occurs earlier during the third trimester of pregnancies of West African women compared with those in North America. This, however, had not been confirmed by other studies.

Local differences in the incidence of RDS between white and black infants, when compared only in terms of birthweight, would not take into account the fact that a large number of black infants are growth retarded. In order to show a true difference in the incidence of RDS, gestational age needed to be assessed accurately for a valid comparison. The vast majority of infants admitted to the neonatal unit at Johannesburg Hospital until the end of the 1980s were

white and, since a computerised data base had been in use for a number of years, data on the incidence of RDS in white low birthweight infants could be extracted retrospectively. A prospective study on black low birthweight infants at Baragwanath Hospital with careful documentation of birthweight, gestation and the presence of RDS was planned in order to compare the incidence of RDS between black and white low birthweight infants in the Johannesburg area.

4.3 The Incidence of Periventricular-Intraventricular Haemorrhage

Periventricular-intraventricular haemorrhage (PV-IVH), defined as haemorrhage into the germinal matrix tissues with or without extension into the ventricular system and involvement of the cerebral parenchyma, remained a common problem in preterm infants (Volpe, 1989a; Volpe, 1989b; Pape, 1989). This lesion was important not only because of its high incidence and the serious nature of the larger haemorrhages, but also because major brain injury in premature infants usually occurred in the context of PV-IVH, either as an apparent consequence of the haemorrhage or as an associated finding (Volpe, 1989a). The pathogenesis of PV-IVH is multifactorial, and different combinations of factors may be operative in different patients (Volpe, 1989b).

One of the earliest definitive reports on the incidence of PV-IVH in VLBW infants by Papile *et al* (1978) utilised computerised tomography scanning to diagnose the lesions. In the ensuing years, however, ultrasonographic transfontanelle sector scanning with a real-time machine became accepted as the best technique for neonatal brain imaging, since good quality serial scans could be obtained at the bedside with minimal disruption to the care of the infant and

without the risks of ionising radiation. This made the detection, staging and follow-up of PV-IVH reliable and cranial ultrasonography became a routine screening procedure in VLBW infants in most neonatal units (Bauchner *et al,* 1988; Farrell and Birnholz, 1987; Grant *et al,* 1988; Graziani *et al,* 1985; Levene *et al,* 1985). The usual reported incidence of PV-IVH in VLBW infants was 30-50% over this time and variations in the incidence between institutions could be explained by differences in populations studied, varying definitions of abnormality, the timing and nature of ultrasound evaluation, and possibly different obstetric and neonatal practices in various centres (Ahmann *et al,* 1980; Dolfin *et al,* 1983; Papile *et al,* 1978; Volpe, 1987; Volpe 1989c).

However, by the end of the 1980s, it appeared that the incidence of PV-IVH in some centres was decreasing. This was so in spite of the fact that survival rates for premature infants, particularly those weighing <1000g at birth, were increasing and the incidence of PV-IVH correlated directly with increasing prematurity. For example, Volpe (1989a) reported a PV-IVH incidence of only 17% for infants with birthweight between 1001g and 1500g, while Philip *et al* (1989) reported an incidence of 25%. In both cases these figures were lower than previously reported from the same centres and it appeared that better overall perinatal care was responsible for these reductions.

Since most pregnant women utilising the antenatal services at Baragwanath Hospital and the Soweto Clinics usually only attended for the first time during the third trimester of pregnancy, a large number of women delivering premature infants either did not attend antenatal clinic at all or had only attended once. Furthermore, they often presented to the hospital in advanced premature labour and delivered within a short period of time while, in addition, the hospital

was frequently overcrowded resulting in less individualised peripartum care. These factors would be expected to increase the incidence of PV-IVH in low birthweight infants. A previous study on the effects of the timing of umbilical cord clamping had indeed suggested a relatively high incidence of PV-IVH among a group of larger low birthweight infants at Baragwanath Hospital (Hofmeyr *et al,* 1988), but no systematic studies on the incidence of PV-IVH in low birthweight infants at Baragwanath Hospital had been done due to the fact that a dedicated ultrasound machine was not available to the neonatal unit in order to study the large numbers of low birthweight infants admitted to the unit. With the acquisition of a new ultrasound machine in 1989, such a study became feasible.

4.4 The Early Effects of Intrauterine Growth Retardation on Low Birthweight Infants

The effects of suboptimal intrauterine growth on low birthweight infants had been the subject of a number of studies and conflicting data had been reported in the literature. Of particular interest was how intrauterine growth retardation (IUGR) may influence two of the major causes of morbidity and mortality in low birthweight infants mentioned above, namely RDS and PV-IVH. It had been suggested that infants with IUGR may be more 'stressed' than those who are appropriately grown and that this in turn resulted in protection against RDS (Gluck and Kulovich, 1973; Procianoy *et al,* 1980), while other studies had indicated that IUGR had no effect on the severity of lung disease or may even result in the need for longer ventilatory support than required for appropriately grown infants (Brownlee *et al,* 1991; Morley *et al,* 1990). Similarly, with regard to PV-IVH, studies had shown that intrauterine growth

retardation may be either protective or an additional risk factor (Bada *et al,* 1984; Heinonen *et al,* 1985; Pena *et al,* 1988; Procianoy *et al,* 1980).

With the high rate of IUGR described by Stein and Ellis (1974) amongst low birthweight infants at Baragwanath Hospital, the effects of IUGR on RDS and PV-IVH needed to be systematically studied.

4.5. Investigation of Alternative Therapies for Infants <1000g at Birth

Although the NICU had increased its capacity by 1988 so that 12 infants could be offered mechanical ventilation at a time, the large numbers of infants of all weight categories who required NICU care resulted in a continuation of the policy which precluded infants <1000g at birth from being offered ventilation. Although this policy had been subjected to extensive debate and alternative ways of selecting infants for ventilation had been investigated, this weight cutoff remained the most practical way of utilising the limited NICU resources available. Facilities available for low birthweight infants in Soweto (and indeed for the whole population of Soweto) were far better than those available for large parts of the country and a national shift in emphasis away from tertiary care towards primary and secondary care facilities had begun. It was clear that facilities in the NICU at Baragwanath Hospital would not be expanded in the foreseeable future and it therefore seemed worthwhile to explore other modalities of therapy that could improve the high mortality of this group of infants.

Since the studies of Liggins and Howie (1972), the use of antenatal steroids had become well

established for the prevention of RDS in premature infants (Avery, 1984; Collaborative Group on Antenatal Steroid Therapy, 1981; Farrel *et al,* 1989; Gamsu *et al,* 1989). Subsequently it was shown by Mammel *et al* (1983) and Avery *et al* (1985) that dexamethasone could be used successfully to improve the pulmonary status of ventilated preterm infants with chronic lung disease, while further studies suggested that early administration of dexamethasone to ventilated preterm infants from the first postnatal day resulted in shorter ventilation periods and a decrease in the incidence and severity of chronic lung disease (Cummings *et al,* 1989; Goldstein *et al,* 1989; Yeh *et al,* 1990). There was only one reported randomised study on the administration of postnatal steroids to premature infants with RDS in the immediate postnatal period without ventilatory support (Baden *et al,* 1972; Soll in l McQueen, 1992). That study failed to show any improvement in outcome for premature infants with RDS, although hydrocortisone was given for one day only. In view of the paucity of research in this area and the reported success of early postnatal dexamethasone in ventilated infants, it seemed appropriate to conduct a trial on the administration of a course of dexamethasone to non-ventilated infants with birthweight <1000g to determine if an improvement in outcome could be achieved.

4.6 Long Term Outcome of VLBW Infants Discharged from Baragwanath Hospital

As discussed in Chapter 2, an extensive review of the literature of English language publications by Escobar *et al* (1991) up to 1988 failed to find any studies from developing countries on the long term outcome of VLBW infants that gave sufficient information from

which the rate of overall handicap and/or cerebral palsy could be derived. The data from developed countries could not readily be extrapolated due to a number of factors prevailing in developing countries which may have significant effects on later growth and development. These include the vastly different availability of intensive care facilities, the high rates of intrauterine growth retardation in developing countries and the extremely poor socioeconomic conditions under which many surviving VLBW infants live.

Long term local follow-up data on surviving VLBW infants were essential for a number of reasons:

a. They would provide an opportunity to assess and review the neonatal practices of the unit.

b. Risk factors for later handicap, including socio-demographic, perinatal and postnatal variables could be assessed as predictors of later outcome.

c. The current selection criteria for admission to the NICU could be assessed in the light of the long term follow-up data.

d. Long term handicap rates needed to be assessed in the light of an often overcrowded unit with what was generally regarded as inadequate staff to patient ratios.

e. Future planning of perinatal services as well as those for children with disability and handicap would benefit greatly from these data.

f. They would provide important additional information on the debates conducted around the provision of maternity and neonatal services in relation to services for other groups in society.

Thus, a long term follow-up study on a cohort of VLBW infants was planned. At that time a group of investigators was planning a large birth cohort study that was to become known as the Birth to Ten study. All infants born over a six-week period in the greater Johannesburg area including Soweto were to be followed for ten years. The study arose from concern over the rapid rate of urbanisation in South Africa and its implications for the health and well-being of children (Yach *et al,* 1991). The overall aim was to determine the biological, environmental, economic and psychological factors that were associated with the survival, health, growth and development of children living in an urban environment (Richter *et al,* 1995). Since a six-week period would be far too short a period to enrol significant numbers of VLBW infants, especially those requiring mechanical ventilation and those less than 1000g at birth who were expected to have high mortality rates, the Birth to Ten study could not provide answers to the above questions with regard to VLBW infants. Nevertheless, it would provide important baseline information regarding children born in an urban environment with which to compare those with VLBW.

A long term follow-up study on a large group of VLBW infants was therefore planned to run concurrently with the Birth to Ten study. Although the group of VLBW infants would also be followed for ten years, for the purposes of this thesis, it was decided to include growth and development for the first five years only.

4.7 Conclusions

In spite of extremely impressive advances in the clinical management of VLBW infants at Baragwanath Hospital, research into many of the issues that had been extensively investigated in other parts of the world had not yet been performed. This series of research projects was thus to be initiated.

Chapter 5

Results of in-Hospital Studies on Low Birthweight and VLBW Infants

Preamble

The series of studies described in this chapter deal with VLBW infants during their initial hospital stay. All of the studies were planned by the author. The first section deals with the survival of VLBW infants at Baragwanath Hospital and is based on the computerised data collection system that was planned and implemented by the author with the assistance of Dr Stephen Wainer as described in Chapter 3. The next three sections deal with data collected prospectively on a cohort of low birthweight infants to study the incidence of and risk factors for RDS and PV-IVH at Baragwanath Hospital. The data on RDS, which were collected while the author was head of the Baragwanath Neonatal Unit, were compared with retrospective data collected on white low birthweight infants admitted to Johannesburg Hospital while the author was a neonatologist at that hospital. The sections on the incidence of PV-IVH and the steroid intervention study were carried out in conjunction with Drs Sandler and Shipalana respectively. In both cases the data were extensively analysed and the manuscripts were largely written by this author for the journal publications that followed and for the data which appear in this thesis. Statistical assistance was obtained from Dr Jackie Galpin of the Department of Statistics at the University of the Witwatersrand for the section on the early effects of IUGR on low birthweight infants. The remainder of the data capture, statistical analysis and preparation of the papers which emanated from these studies were the responsibility of the author.

All of these studies were approved by the Committee for Research on Human Subjects of the University of the Witwatersrand and, except where routine data was being collected, informed consent was obtained from the parents of the infants studied.

5.1. Survival of VLBW Infants at Baragwanath Hospital

As discussed earlier, the survival of VLBW infants was described in the early years after the opening of the neonatal unit at Baragwanath Hospital by Kahn *et al* (1954). Later, Rissik (1983) set up a detailed manual system of data collection which allowed analysis of the survival of low birthweight infants in detail in the early 1980s. Subsequently a computerised data base was established and was able to provide neonatal statistics from 1990, the first year when all neonatal admissions were computerised. The changes in mortality of low birthweight infants over time were assessed and data for the two year periods 1990-1991 and 1995-1996 were compared with the results obtained from the earlier years.

5.1.1 Methods

A brief description of the overall care of low birthweight infants during the period of this series of studies, namely 1989 to 1996, is presented. Low birthweight infants were initially admitted to a nursery in the labour ward area where they were resuscitated if necessary and their clinical condition stabilised. Infants with birthweight less than 1000g, those with lethal congenital abnormalities or abnormalities/complications considered not to be compatible with

a reasonable long term prognosis such as those with major intracranial haemorrhage, were not considered for admission to the NICU. For all others, criteria for admission to the NICU for ventilatory support were as follows:

1. Inability to sustain a pO2 >50mm Hg in 60-80% headbox oxygen.
2. A rising pCO2 >50-55mm Hg.
3. A pH <7.25.
4. Severe apnoea.

If the infant met one of these criteria, he/she was admitted for ventilatory support. Ventilation was carried out with time cycled, pressure limited neonatal ventilators adhering broadly to the strategies outlined by Carlo and Martin (1986). Infants were nursed under radiant warmers for the duration of their NICU stay and usually had arterial (umbilical or peripheral) and peripheral venous catheters placed. Antibiotics, pressors and other medications such as indomethacin were used according to standard indications. Artificial surfactant was used after its introduction in late 1991 according to protocols outlined by Ballot *et al* (1995a).

VLBW infants not requiring ventilatory support were usually admitted to the high care area where they were nursed in closed incubators, given oxygen via headbox or into the incubator as indicated and received general care and medications as required. Pulse oximetry was not available at that time and oxygen therapy was determined by periodic blood gas analysis. Once their condition was stabilised, their oxygen requirement was <30%, enteral feeds had been successfully initiated and their weight reached 1200g, they were transferred to an intermediate care ward where antibiotics and other medications were continued until no longer

indicated, enteral feeds were further increased until intravenous fluids could be discontinued and growth was monitored. During their hospital stay, VLBW infants received expressed own-mother's milk whenever possible and >90% of mothers provided milk for their infants. This was supplemented with one of the commercially available premature infant formulas as necessary. Feeds were adjusted to provide infants with 120 kcal/kg/day. When they had reached a size and maturity such that they no longer required oxygen or incubator care, were on full enteral feeds and had achieved a weight of 1600g, they were transferred to a low care ward where the mothers were more intimately involved in the care of their infants. Infants were discharged when they were able to suck adequately from the breast or bottle, had no residual clinical problems requiring hospital care and had achieved a weight of 1700-1900g.

Chi-square analysis was performed in order to compare survival of VLBW infants at different time periods.

5.1.2. Results

During 1990, the year in which the greatest number of deliveries occurred, a total of 20175 deliveries took place at Baragwanath Hospital, 12197 deliveries in the Soweto Clinics and 3497 infants were born outside of the health care system, but were brought within 24 hours of birth (this latter group was usually referred to as born before arrival or BBA). This gave a figure of 35869 deliveries during the year. Of these 677 were VLBW (1.9%) of whom 111 had a birthweight <1000g. However, due to the opening up of other hospitals in Johannesburg for black infants, the total delivery number fell significantly after 1990 so that within a few years, delivery numbers had fallen by one third. Noteworthy, however, was that the numbers of

VLBW infants did not change significantly, but, following the introduction of free maternal care in mid-1994, the number of BBA infants fell dramatically. These data are reflected in Table 5.1.

Table 5.1 Total number of deliveries in the Baragwanath Hospital/Soweto Clinic complex and total numbers of VLBW infants admitted 1990-1996

Year	Deliveries (No)				Total of VLBW Infants (%)
	Hospital	Clinics	BBA	Total	
1990	20 175	12 197	3 497	35 869	677 (1.9)
1991	18 521	11 243	3 347	33 111	624 (1.9)
1992	17 319	9 823	3 268	30 410	661 (2.2)
1993	15 452	8 944	3 043	27 439	689 (2.5)
1994	15 731	7 719	1 949	25 399	637 (2.5)
1995	16 460	7 380	720	24 560	572 (2.3)
1996	15 835	7 710	515	24 060	606 (2.5)

The survival of low birthweight infants with birthweight <2000g over three time periods of two years each, 1981-1982, 1990-1992 and 1995-1996 were analysed and the results are reflected in Table 5.2. It can be seen that there was a significant increase in survival for infants with birthweight 1000g to 1499g between each time period, while the increase in survival for those <1000g was significant between 1981/82 and 1990/91, but just failed to reach significance for the period between 1990/91 and 1995/96 (p=0.053). This was in spite of the fact that infants with birthweight <1000g were still seldom ventilated.

Table 5.2 Survival of low birthweight infants <2000g at birth over three time periods between 1981 and 1996

Birthweight (g)	1981-1982	1990-1991	1995-1996
<1000g	13.9%	23.9%*	31.6%
1000-1499g	63.6%	70.1%**	79.1%**
1500-1999g	91.6%	91.8%	93.8%

* p=0.027 compared with previous time period

** p<0.01 compared with previous time period

The figures reported by Rissik (1983) for the 1981/82 time period did not divide the weight groups into smaller categories. However, with a computerised data base from 1990, it was possible to analyse survival by 100g weight categories, comparing the time periods 1990/91 and 1995/96. For infants <700g at birth there were only occasional survivors while survival remained at 20% for those 700-800g at birth during both time periods. However, it can be seen in Figure 5.1 that, for each 100g category between 800g and 1300g, there appeared to be an increase in survival between the two time periods of 10-15%, although this difference was only statistically significant for the 100g categories between 1000g and 1300g birthweight ($p<0.05$ or lower). Survival for infants above 1300g, already more than 80% in the time period 1990/91, did not increase significantly.

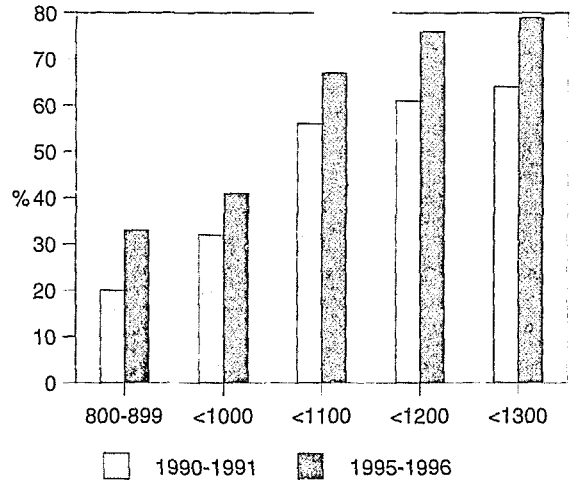


Figure 5.1 Comparison of survival (%) of VLBW infants between 1990-1991 and 1995-1996 by 100g birthweight categories

To illustrate the improvement in survival of VLBW infants since the early 1950s, figures for 1995/96 were compared with those originally reported by Kahn *et al* (1954) and, since the original report was in pounds and ounces, the 1995/96 figures were analysed accordingly. The results are shown in Table 5.3.

Table 5.3 Comparison of the survival of VLBW infants born in 1951/52 with those born in 1995/96

Birthweight	1951-52	1995-96
<907g	2%	25.4%
907-1355g	25%	71.5%

Note: 907g = 2lbs and 1355g = 3lbs.

5.1.3 Discussion

Clearly there has been a dramatic improvement in the survival figures of VLBW infants over the past five decades. As shown in Chapter 3, the increased survival during the first three decades was across the weight spectrum of low birthweight infants and corresponded with improvements in the overall care and management of these infants as incubators, better methods of oxygen delivery and fluid and nutritional management were introduced. Since 1981, however, the improvement has been confined to those with a birthweight <1500g. While the improvement in survival could be attributed to the development of the NICU in the case of infants 1000-1499g, this cannot be the explanation for the improvement in survival of those <1000g since they were seldom offered mechanical ventilation.

The explanation would appear to be a more complex one. There can be no doubt that the NICU had a direct effect in reducing the mortality of infants between 1000g and 1499g. To illustrate this, as will be seen later in the results presented in this thesis, during 1990 a total of 241 infants in this birthweight range were ventilated of whom 103 survived and there was an overall survival of 66% for all infants with birthweight 1000-1499g. Due to the strict criteria utilised for selection for admission to the NICU, it is probable that the majority of the NICU survivors would not have survived without mechanical ventilation and that the overall survival would have been at least 10% lower. However, the concomitant improvement in survival for those <1000g at birth is more difficult to explain. It was strongly felt at the time that the NICU was opened in 1979 that the effects of its opening were not restricted only to those who were admitted to the unit, but that it had a ripple effect on the care of infants throughout the neonatal wards. The knowledge that infants could be admitted for ventilatory support should this be

required was felt at the time to result in a general improvement in the standards of care at all levels (Prof K.D. Bolton, personal communication) and, even though ventilatory support was not offered to infants <1000g the improved general standards of care probably affected the overall care that was offered to these infants.

The effects of having an NICU also influenced obstetric practice with the result that the management of premature deliveries became more active, especially between the periods 1990/91 and 1995/96. The benefits of antenatal steroids had been known for many years. However, since many women were admitted to the hospital already in advanced premature labour, this meant that the window of opportunity for administration of antenatal steroids was often not available. There was also reluctance to offer antenatal steroids to women with pregnancy induced hypertension due to the concern that this might aggravate the maternal hypertension, and in cases where there was premature rupture of membranes, there was concern that antenatal steroids might potentiate infectious complications in the mother and fetus/neonate. The Conferences on Priorities in Perinatal Care resulted in sharing of information and experience as well as collaborative studies to investigate issues such as these. The result was that, over time, the use of antenatal steroids became more liberal during the 1990s and this presumably also contributed to the improvement in outcome of VLBW infants with birthweight both less than and greater than 1000g.

The impact of artificial surfactant was not systematically studied, but most randomised controlled studies and meta-analyses showed an increase in survival in those infants who were treated with surfactant (Soll *et al*, 1990; Avery and Merrit, 1991; Soll and McQueen, 1992). In addition, the introduction of artificial surfactant into routine clinical care coincided with an

improvement in survival of VLBW infants in developed countries and it was widely believed that artificial surfactant was one of the main contributing factors, as previously discussed in Chapter 2 (Schwartz *et al,* 1994). Thus, although artificial surfactant was used far less freely in the public sector hospitals in South Africa than was the case in developed countries and in the private sector in South Africa (Davies *et al,* 1995a), it is probable that its use contributed to the improved survival of VLBW infants. It is noteworthy that the greatest improvement in survival between 1990/91 and 1995/96 was in infants with a birthweight between 1000g and 1300g and, as demonstrated in the next section (see Figure 5.2), it was in this group that surfactant would be expected to be most useful.

When comparing the 1995/96 figures for the survival of VLBW infants with those from the early 1950s, the enormous progress that has been made in the care of VLBW infants is apparent. Even in the relatively short period of 15 years since 1981, the improvement in survival is impressive and is still ongoing. As with most areas of progress in medical science, it is seldom one particular factor, in this case the introduction of mechanical ventilation or the use of artificial surfactant, that is solely responsible for overall improvements in outcome, but it is a combination of many different factors amongst which some may be more important than others. There is no doubt that factors such as mechanical ventilation and artificial surfactant were very important, but the improvements in care of the mother during the antenatal and perinatal periods and the general supportive care of VLBW infants at all levels in the neonatal wards were likely to have been equally important.

5.2. The Incidence of RDS in Black and White Low Birthweight Infants (Cooper *et al,* 1994)

As discussed in Chapter 4, it was generally accepted that premature black infants were at lower risk for developing RDS when compared with white infants of the same gestation. However, apart from studies in Cape Town in the early 1970s which compared mainly white infants with those of mixed race and included very few black infants (Malan *et al,* 1974; Rush and Segall, 1978), this had never been studied systematically in South Africa and no data were available from Johannesburg. The purpose of this study was therefore to compare the incidence of RDS in black and white low birthweight infants in Johannesburg.

5.2.1 Methods

Infants with birthweight 1000-1749g were the subjects of this study. Black infants were prospectively enrolled from admissions to the neonatal unit at Baragwanath Hospital, while white infants were identified from a retrospective survey of admissions to the unit at Johannesburg Hospital.

5.2.1.1 Baragwanath Hospital Cohort

Infants with birthweight 1000-1749g admitted to the Baragwanath Hospital neonatal unit from the beginning of August to mid-December 1989 were enrolled. Since any infant born at one of the Soweto maternity clinics weighing <1750g at birth was immediately referred to the hospital and there were no recorded deaths of such infants at any of the clinics over the study

period, clinic deliveries were included in this study since no selection bias was felt to be present. However, infants transferred to the unit from outside hospitals or born at home were excluded due to potential selection bias. Of the 305 infants within this weight range admitted to the unit over this time period, 48 were thus excluded. The upper birthweight limit for this study was set at 1749g as infants above this weight were not necessarily admitted to the neonatal wards if they had no complications, but were rather sent to the postnatal wards for rooming in with their mothers and received care similar to larger well babies. The lower limit of 1000g was set as it would have been difficult to document the occurrence of RDS in infants who were not offered mechanical ventilation and frequently died soon after birth.

Since accurate information on maternal dates and early obstetric ultrasound findings to assess gestational age were not routinely available, gestational age was assessed by the Ballard score (Ballard *et al*, 1979). Ballard scores were performed by two investigators who had previously shown a good correlation in their assessments. Infants were classified as SGA on the basis of a birthweight below the 10th percentile on the Lubchenco growth curve (Lubchenco *et al*, 1963a). All chest radiographs were reviewed jointly by three neonatologists who were unaware of the clinical and laboratory findings. The diagnosis of RDS was made on the basis of respiratory distress developing in the first 6-12 hours after birth, a chest radiograph showing a diffuse reticulo-granular pattern in both lung fields with air bronchograms and no laboratory evidence of infection. Ten infants who required mechanical ventilation due to early onset respiratory distress died before a chest radiograph could be obtained. None of these infants had positive blood cultures or other evidence suggestive of infection and their diagnosis was assumed to be that of RDS. In some instances, infants with mild respiratory distress which resolved within 48 hours were not radiographed. They were assumed to have transient

tachypnoea of the newborn and excluded since none of the proven cases of RDS in this study had resolved so rapidly.

5.2.1.2 Johannesburg Hospital Cohort

A retrospective search of all infants weighing 1000-1749g admitted to the neonatal unit of Johannesburg Hospital over a six and one-half year period from January 1983 until mid-1989 was performed on the computerised neonatal data base. Again, to exclude bias, only inborn infants were selected for inclusion in this study. This hospital had between 2000 and 2500 inborn deliveries annually over this period. Gestational age had been recorded as the best estimate from antenatal data (maternal dates and early antenatal sonar) and postnatal examination using Dubowitz (Dubowitz *et al*, 1970) or Ballard scores. The diagnosis of RDS had been made using the same criteria as that described for the Baragwanath cohort and similar clinical and laboratory data were utilised.

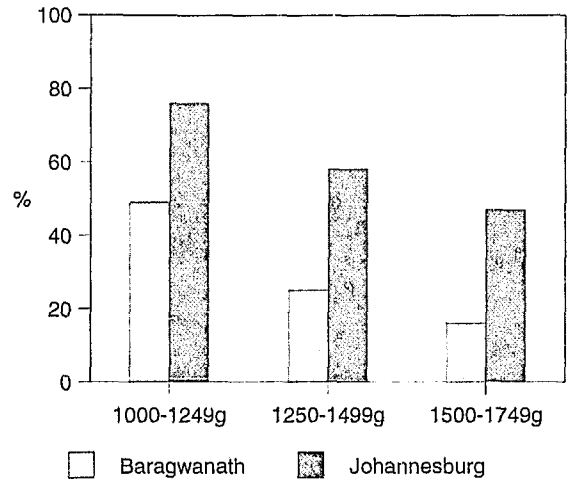
Although the chest radiographs were not reviewed specifically for this study, one paediatric radiologist reported on the vast majority of the chest radiographs over this time period. Data from both cohorts were computerised and analysed using the Epi Info program (Dean *et al*, 1990). Statistical analysis of data was performed by using chi-square analysis; where an expected cell was <5, Fisher's exact test was used.

5.2.2 Results

A total of 257 black infants born at the hospital or one of the Soweto clinics formed the

Baragwanath cohort and 358 inborn white infants formed the Johannesburg cohort. They were divided into 250g weight categories and two week gestational age categories. There were no significant differences between the distribution of infants in the three weight categories, but the Baragwanath cohort had significantly higher gestational ages ($p<0.001$ for comparison of gestational age distribution). Thus the Baragwanath cohort was more mature at a given birthweight than those at Johannesburg Hospital. Correspondingly, 131 (51.0%) of the 257 Baragwanath infants were SGA according to Lubchenco's growth charts, while only 113 (36.6%) of the 358 making up the Johannesburg cohort were SGA ($p<0.001$, odds ratio 2.25; 95% CI 1.6-3.18).

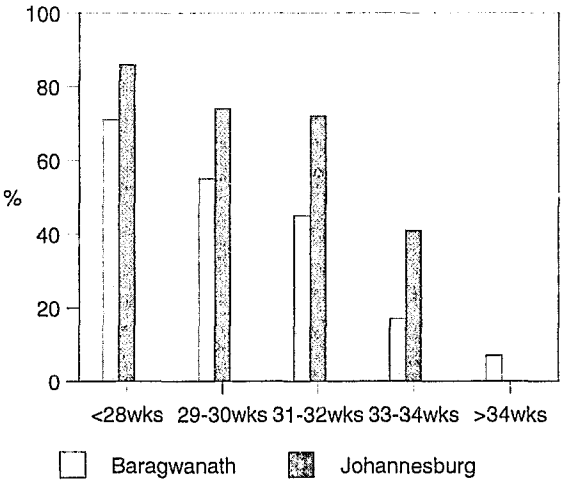
The overall incidence of RDS for the entire cohort was 30.8% for black infants and 57.8% for white infants ($p<0.001$, odds ratio 0.32; 95% CI 0.23-0.46). Figure 5.2 shows the comparison of the incidence of RDS according to the three weight categories. It can be seen that RDS was diagnosed significantly more frequently in white infants in each of the weight categories.



p<0.001 for comparisons of each birthweight category

Figure 5.2 Incidence of RDS by birthweight at Baragwanath and Johannesburg Hospitals

Although this could be partially explained by the greater maturity of the black infants, Figure 5.3 shows that in each two week period between 29 and 34 weeks of gestation black infants were significantly less likely to develop RDS than white infants. For infants 29-34 weeks of gestation, 36.2% of black infants and 62.5% of white infants were diagnosed as having RDS ($p<0.001$, odds ratio 0.34; 95% CI 0.23-0.51).



$p < 0.05$ or lower for all comparisons between 29 and 34 weeks of gestation

Figure 5.3 Incidence of RDS by gestation at Baragwanath and Johannesburg Hospitals

5.2.3 Discussion

This study showed that black infants at Baragwanath Hospital weighing 1000-1750g at birth were generally more mature than white infants at Johannesburg Hospital and had a higher incidence of IUGR. This was an expected finding and partially explained the lower incidence of RDS in the Baragwanath group as a whole as well as in the weight subgroups. However, while white infants in this study appeared to have an incidence of RDS similar to that described for white low birthweight infants in other parts of the world (Farrell and Avery, 1975; Gluck, 1979; Liggens and Howie, 1972; Usher *et al,* 1971), the incidence of RDS was clearly lower in black infants between 29 and 34 weeks of gestation when compared with

white infants regardless of birthweight. While this difference was in keeping with other studies, the explanation for this difference is not clear. It should be noted that the mothers of the Baragwanath infants generally had far less antenatal care (54% of the cohort had not attended antenatal clinics), often arrived at the hospital in advanced premature labour, seldom received antenatal steroids and the infants were frequently asphyxiated at birth. These factors would all have been expected to increase the incidence of RDS rather than decrease it as shown in this study (Caspi *et al,* 1981; Jones *et al,* 1975). Studies on the relationship between intrauterine growth retardation and RDS are conflicting with some studies suggesting that growth retardation may be protective against RDS while others have suggested that it may be an aggravating factor as previously discussed. In order to examine this, a more detailed analysis on the effects of intrauterine growth retardation on low birthweight infants with regard to a number of clinical complications was subsequently performed and is presented later in section 5.4.

This study also provided important baseline information in the South African context for the rational use of artificial surfactant for the prophylaxis and/or rescue treatment of RDS, since artificial surfactant had not been introduced into the country at that time. For black infants <29 weeks gestation in this study, only 43% required ventilation during the first 48 hours of life for RDS, while this was true for only 30% of those 29-30 weeks gestation. Since few hospitals in this country routinely ventilated infants <1000g (the lower cutoff weight for this study), prophylactic use of artificial surfactant for black infants did not appear to be warranted. While the incidence of RDS in white infants in this study was higher, it is noteworthy that the mortality was low (11.7% overall) and routine use of prophylactic surfactant at birth would have resulted in a large number of infants deriving little benefit. Thus for infants >1000g at

birth in South Africa, it seemed advisable to reserve the use of artificial surfactant for rescue treatment once a definite diagnosis of RDS had been made, especially in view of the very high cost of the product. Using data from this study and others, strategies for the rational use of artificial surfactant when it was subsequently introduced into South Africa were designed and tested in a variety of clinical settings and formed the basis of several reports by Davies, Ballot and Rothberg (Davies *et al*, 1995b; Ballot *et al,* 1995a; Ballot *et al,* 1995b).

In conclusion this study, which was conducted at two hospitals in the Johannesburg area, showed a significantly lower incidence of RDS in black infants weighing 1000-1749g at birth and those 29-34 weeks gestation when compared with white infants. This confirmed data from other parts of South Africa and elsewhere in the world, but the reasons for these differences were not clear and warranted further study.

5.3 The Incidence of PV-IVH (Sandler *et al,* 1994)

As discussed in Chapter 4, a previous study had suggested that the incidence of PV-IVH in premature infants at Baragwanath Hospital was relatively high (Hofmeyr *et al,* 1988), but no systematic evaluation of the incidence of PV-IVH had been performed due to the fact that a dedicated ultrasound machine was not available to the neonatal unit in order to study the large numbers of low birthweight infants. With the acquisition of a new ultrasound machine in 1989, such a study became feasible.

The purpose of this study was to describe the incidence, severity and short term sequelae of

PV-IVH in a defined group of low birthweight infants at Baragwanath Hospital and to compare these findings with other reported studies.

5.3.1 *Methods*

The cohort of infants studied was the same as that of the Baragwanath cohort studied with respect to the incidence of RDS. Thus over the four and a half month period mentioned previously, all infants with a birthweight between 1000g and 1749g admitted to the neonatal unit at Baragwanath Hospital were eligible for this study. For this part of the study, outborn infants and those born at home were included since these were regarded as potential risk factors to be examined. However, infants with severe congenital abnormalities and those infants dying before a cranial ultrasound examination could be performed (this occurred particularly after hours) were excluded from subsequent analysis. All relevant information relating to demographic factors, clinical details and laboratory investigations was documented prospectively for subsequent analysis of risk factors for PV-IVH in this population.

Diagnosis of PV-IVH was made by transfontanelle real-time ultrasound examination, using a portable Kretztechnic Combison 310 sector scanner with a 7.5 MHz transducer. Ultrasound examinations were performed by three members of the neonatal division. During each ultrasound scan, coronal and parasagittal views were visualised and at least one image in each plane was photographically recorded. A final decision regarding the grade of PV-IVH for each infant was reached by consensus of all three sonographers. The most severe grade of PV-IVH recorded was used for each infant. To enable comparison with previous studies, Papile's classification (Papile *et al*, 1978) of PV-IVH was used as this still appeared to be the grading

system most widely employed, despite certain limitations. In this classification:

Grade I constitutes germinal matrix bleeding only

Grade II bleeding into one or both lateral ventricles

Grade III sufficient bleeding into the lateral ventricles to cause acute ventricular dilatation

Grade IV associated intracerebral bleeding.

Periventricular echodensities were recorded, but, since about 85% of these resolve without apparent sequelae, only those resulting in cystic periventricular leukomalacia (PVL) as described by Van de Bor *et al* (1989) were subsequently analysed in detail. Every surviving infant had at least one ultrasound scan at 7-10 days of age. Due to limitations of time and access to the ultrasound machine and the large number of infants studied over a relatively short period, it was not possible to do ultrasound scans earlier and more frequently on all infants. However, all infants who required mechanical ventilation and one third of the infants who did not require mechanical ventilation, allocated by random number generation, had ultrasound scans on at least three occasions at three, seven and 14 days of age. Ultrasound scans were done at any stage if clinically indicated and all infants with demonstrated PV-IVH were subsequently scanned every 7-14 days to detect the development of sequelae such as post haemorrhagic ventricular dilatation and PVL. Wherever possible, infants had a follow-up sonar at 40 weeks post conceptual age. This was done either before hospital discharge or at the first neonatal follow-up appointment.

All data were entered onto a microcomputer and analysed using the Epi Info program (Dean *et al*, 1990). Statistical analysis of data was performed by using chi-square analysis for

discrete variables; when an expected cell was <5, Fisher's exact test was used. When multiple intergroup comparisons were done, the usual significance level of 0.05 was adjusted by using the Bonferroni correction. To assess risk factors for PV-IVH, a univariate analysis was initially performed using the grade of PV-IVH as the dependent variable. This was then analysed further using multiple linear regression analysis.

5.3.2 Results

A total of 305 infants with birthweights 1000-1749g were enrolled over the period from the beginning of August to mid-December 1989. Fifteen infants died before a cranial ultrasound examination could be performed, ten of whom died within 24 hours of birth. An additional eight infants had major congenital abnormalities and all but one of these infants died. In terms of the study protocol, these 23 infants were excluded from further analysis. The study population thus consisted of 282 infants. All of the 68 infants who required mechanical ventilation within 48 hours of birth had their first ultrasound scan by the third day of life with a minimum of two repeat scans at one and two weeks of age (unless they died earlier). According to the protocol, 79 of the 214 non-ventilated infants were randomly assigned to have ultrasound scans on days three, seven and 14, while a further 18 infants had early scans for clinical indications. The remaining 117 infants had their first scan at age 7-10 days.

Of the 282 study infants, 130 (46.1%) had ultrasound evidence of PV-IVH as shown in Table 5.4, but only 25 (8.9%) had moderate to severe haemorrhages (grades III or IV). Only 125 infants (44.3%) had attended antenatal clinics. Details of the sex, place of birth, numbers of those with birthweight <1500g and gestation <35 weeks and those with intrauterine growth

retardation can be seen in Table 5.4 with the overall incidence of PV-IVH for each group. The incidence of PV-IVH for those <1500g and <35 weeks gestation was 53.3% and 52.1% respectively.

Table 5.4 Details of the study population (incidence of PV-IVH)

	Total		With PV-IVH*	
	No.	%	No.	%
Total cohort	282	100.0	130	46.1
Male	142	50.3	70	49.3
Female	140	49.7	60	42.9
Inborn †	224	79.4	101	45.1
Birthweight < 1500g	184	65.2	98	53.3
Gestation < 35 weeks	215	76.2	112	52.1
SGA	153	54.3	58	37.9

* Number and % with any grade of PV-IVH.

† Of the remaining infants 10 (3.5%) were born at a Soweto clinic, 14 (5.0%) at another hospital or clinic, and 34 (12.1%) at home or *en route* to Baragwanath Hospital.

There were no significant differences for overall incidence or severity of PV-IVH according to sex or place of birth.

Infants were divided into 250g weight categories and also grouped according to gestational age. The distribution of the grades of PV-IVH by weight and gestational age categories is shown in Figures 5.4 and 5.5 As can be seen, the overall incidence and severity of PV-IVH decreased with increasing birthweight and gestation. Of infants <1250g birthweight, 66% had some grade of PV-IVH, compared with 43% for those 1250-1499g ($p<0.01$) and 33% for those 1500-1749g ($p<0.001$). The incidence of moderate-severe PV-IVH (grades III or IV) was 24% for those <1250g at birth and 29% for those <31 weeks gestation compared with only 3% and 4% for those with greater birthweight and gestation respectively ($p<0.001$ for comparisons).

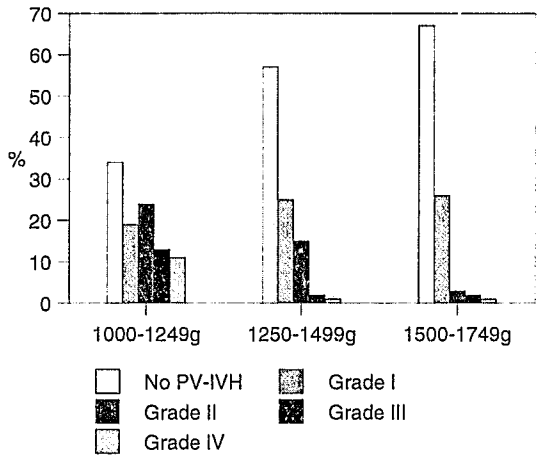


Figure 5.4 Incidence of PV-IVH by birthweight and grade of PV-IVH

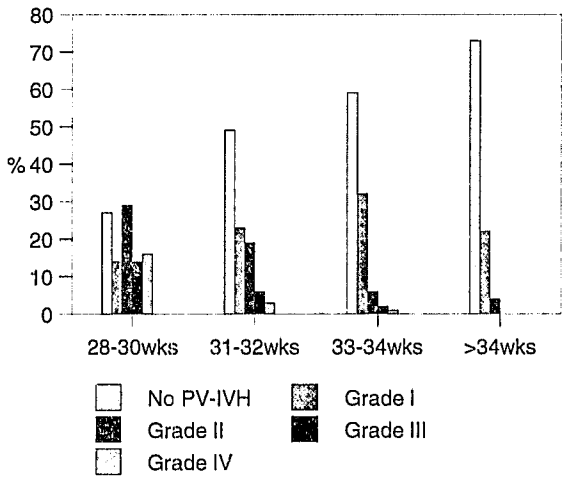


Figure 5.5 Incidence of PV-IVH by gestation and grade of PV-IVH

A number of demographic, clinical and laboratory variables recognised as risk factors for PV-IVH were analysed to see if they applied to our study population (Bada *et al,* 1984; Levene *et al*, 1982; Kauffman, 1986; Pape, 1989; Volpe, 1987). Similar trends existed in the various weight and gestational age groups and therefore the risk factors were analysed for the whole group. In the univariate analysis, lower gestational age and birthweight, a lower five minute Apgar score, the need for active resuscitation at birth, the occurrence and severity of RDS, the requirement for mechanical ventilation in the first 48 hours of life and the development of pneumothorax all showed a significant correlation with the grade of PV-IVH, while IUGR and delivery by caesarean section showed a significant negative correlation ($p<0.05$ in all cases). Outborn infants did not have a significantly higher occurrence or severity of haemorrhage than those born in the hospital. Using multivariate analysis, in addition to gestational age and birthweight, only the need for active resuscitation at birth, the need for mechanical ventilation and the occurrence of pneumothorax were significantly associated with the development and severity of PV-IVH.

Table 5.5 indicates the survival of infants according to the occurrence of PV-IVH. As can be seen survival decreased as the grade of PV-IVH increased and this association was highly significant ($p<0.001$). Only four infants with grade III and one with grade IV PV-IVH survived.

Table 5.5 Outcome according to grade of PV-IVH

Grade of PV-IVH	Total		Survived to hospital discharge	
	No.	%	No.	%
0	152	53.9	141	92.8
I	67	23.8	56	83.6
II	38	13.5	26	68.4
III	14	5.0	4	28.6
IV	11	3.9	1	9.1
Total	282	100	228	80.9

The sonar-detected neuropathological sequelae of PV-IVH in the 228 surviving infants also related to the grade of PV-IVH. Of the babies without PV-IVH the vast majority of survivors, 126 out of 141 (94%), had normal follow-up ultrasound scans at or close to 40 weeks post conceptual age. Of the surviving infants with grade I PV-IVH 55% (31 out of 56) developed germinal matrix cysts on follow-up ultrasounds, while they were found in nine out of 141 surviving infants (6%) with no record of PV-IVH. Approximately 50% of infants with intraventricular bleeding (grade II or more) developed some degree of ventricular enlargement if they survived the initial period, but only six of these infants developed clinical hydrocephalus. In five of these infants the hydrocephalus arrested, while one surviving infant required a ventriculo-peritoneal shunt for posthaemorrhagic hydrocephalus. Generally, ventricular dilatation appeared to reach a maximum between one and two weeks after the initial bleed and then settled over the next one to two months. Five infants out of 141 with no previously documented intraventricular bleeding developed mild, non-progressive ventricular

dilatation. Only three infants who survived to hospital discharge had definite cystic PVL documented (two of these originally had grade I and one had grade III PV-IVH). PVL had also been noted in six of the 54 infants who died. Three of these infants had grade III haemorrhage and three had grade IV PV-IVH. The only surviving infant who developed a large porencephalic cyst as defined by Volpe (1987) was the infant who had sustained a grade IV haemorrhage and survived.

5.3.3 Discussion

The usual reported incidence of PV-IVH in infants <1500g at birth was 30-50% (Ahmann *et al*, 1980; Dolfin *et al,* 1983; Papile *et al*, 1978; Volpe, 1987), but the incidence of PV-IVH in major centres appeared to be decreasing by the end of 1980s. For example, Volpe (1989a) reported a PV-IVH incidence of only 17% for infants between 1001-1500g, while Philip *et al* (1989) reported an incidence of 25%. In both cases these were lower than previously reported figures from these centres and it is probable that better perinatal care resulted in these reductions. In this study the incidence of PV-IVH of more than 50% in those 1000-1500g birthweight and <35 weeks gestation was higher than most previously reported studies, all the more so because infants weighing <1000g at birth were not included. While the possibility that this relatively high overall incidence may have been due in part to over diagnosis of subependymal (grade I) haemorrhages cannot be completely ruled out, accepted criteria for diagnosing these lesions were strictly adhered to. In addition, the fact that 55% of all infants with initial grade I haemorrhage later went on to develop subependymal cysts suggests confirmation of the diagnosis of a subependymal bleed in over half of these infants. More than 50% of the mothers of these VLBW infants at Baragwanath Hospital did not attend antenatal

clinics, many arrived at the hospital in advanced premature labour and delivered within a relatively short period of time, there was frequent overcrowding at the hospital and low birthweight infants with respiratory distress may have had to wait longer than would be desirable before being ventilated due to a shortage of ventilator facilities. It is probable that these factors all contributed to a compromise in the condition of many low birthweight infants managed at the hospital and in turn resulted in the high incidence of PV-IVH.

While the relatively high incidence of PV-IVH at Baragwanath Hospital was of concern, the majority of haemorrhages that occurred in this study population were smaller bleeds. In this study, moderate and severe haemorrhage (grades III and IV) occurred in 12.0% of infants <1500g and in 11.6% of infants <35 weeks gestation which was comparable with the reported rates of 6-19%. As seen in Table 5.5, the high incidence of PV-IVH at Baragwanath Hospital was largely due to an excess of grade I PV-IVH in particular and, to a lesser extent, grade II PV-IVH when compared with other reported studies. It has been suggested that there may be different risk factors for germinal matrix haemorrhage on the one hand and intraventricular haemorrhage on the other (Leviton *et al,* 1988). Thus it is possible that conditions in our study population favoured the development of germinal matrix haemorrhage, but not necessarily larger intraventricular bleeds.

As mentioned, multiple risk factors have previously been implicated in the aetiology of PV-IVH in VLBW infants (Bada *et al,* 1984; Levene *et al,* 1982; Kauffman, 1986; Pape, 1989; Volpe, 1987). In this study, factors which did have a significant association with PV-IVH have been found previously. The finding that the need for active resuscitation was significantly associated with PV-IVH even when gestational age and the severity of lung

disease were considered suggests that prevention of birth asphyxia in these infants could result in a reduction in the incidence of PV-IVH. The association between PV-IVH and outborn birth has been consistently reported, but, somewhat surprisingly, this was not the case in this study despite the fact that 59% of the outborn infants were actually born at home. This paradoxical finding may relate to a selection process, whereby only those infants born at home with less serious complications may have reached the hospital.

In summary, there appeared to be a high overall incidence in this study population of PV-IVH, particularly for smaller haemorrhages. Some of the factors responsible for this should be preventable by the application of basic primary and secondary health care measures which would improve the overall quality of perinatal care. With the anticipated improvement in these levels of health care, it will be important to monitor the incidence of PV-IVH in such institutions to see if there is the expected decline.

5.4 The Early Effects of IUGR on Low Birthweight Infants (Cooper *et al,* 1997)

The effects of suboptimal intrauterine growth on low birthweight infants have been the subject of a number of studies and conflicting data have been reported in the literature. Of particular interest is how IUGR may influence two of the major causes of morbidity and mortality in low birthweight infants, namely RDS and the development of PV-IVH. As discussed in Chapter 4, there were conflicting data in the literature regarding the effects of IUGR on the incidence and severity of both RDS and PV-IVH.

5.4.1 Methods

The cohort of infants with birthweight 1000-1749g admitted to the Baragwanath Hospital neonatal unit over a four and a half month period was enrolled as described in the previous two components of this phase of the study. In a study such as this within a defined birthweight range, undergrown infants in the lower gestational age range and better grown infants in the upper range would be excluded. However, analysis of the birthweight and gestational age data showed that almost all infants born at the hospital over this period with a gestation 30 to 32 weeks inclusive were included in the cohort. Thus for the purposes of this analysis, only those 30-32 weeks gestation without major congenital abnormalities were included. Infants born at home or referred from an outside hospital were also excluded due to potential selection bias. Infants were categorised into being SGA if they fell below the 10th percentile of Lubchenco's norms as previously described, while infants who were appropriate for gestational age (AGA) with birthweight >10th percentile were further subdivided into those with birthweight between the 10th and the 25th percentiles, those between the 25th and the 50th and those above the 50th percentile. Furthermore, each infant was assigned a birthweight ratio (BR) which was calculated by dividing the birthweight by the expected weight (50th percentile) for gestational age (Brownlee *et al,* 1991; Morley *et al,* 1990). Length and head circumference were measured by a fibre glass tape measure and were also plotted on the Lubchenco charts.

The main statistical techniques used were analysis of variance (ANOVA), Kruskal Wallis tests, contingency tables and the loglinear model. Continuous variables such as BR were analysed for differences as to factors (such as RDS and PV-IVH grouping) using multifactor ANOVA in cases where checks such as residual plots indicated the viability of the assumption

of the data being normally distributed around the factor means. In cases where this assumption was suspect, the nonparametric Kruskal Wallis test was used. For analyses involving categorical variables such as for mode of delivery, the need for resuscitation at birth and the occurrence of a range of neonatal complications, a loglinear analysis was used, supplemented with contingency table analysis and tests on odds ratios (Christensen, 1990; Upton, 1978).

5.4.2 Results

A total of 104 infants with gestational ages ranging from 30-32 weeks met the criteria for this study. Table 5.6 shows the mean gestational age, birthweight, head circumference and length of these infants. Also shown are the numbers of infants with a birthweight <10th percentile (SGA), between the 10th and 25th percentiles and >25th percentile. Only two (1.9%) of the latter category had a birthweight above the 50th percentile. Four infants did not have length recorded, while three infants did not have head circumference measurements recorded. The mean values for birthweight, head circumference and length fell between the 10th and 25th percentile of Lubchenco's norms and, of those who were SGA, 68% had a head circumference measurement and 58% had a length measurement below the 10th percentile.

Table 5.6 Mean gestational age, birthweight, length and head circumference of study infants (effects of IUGR)

	Percentile of Lubchenco's norms for birthweight			
	Total group	**<10th**	**10th-25th**	**>25th**
Gestational age (wks)	104 31.2 ± 0.38	25 31.3 ± 0.80	43 31.1 ± 0.88	36 31.2 ± 0.82
Birthweight (g)	104 1 320 ± 182	25 1 118 ± 83	43 1 297 ± 121	36 1 486 ± 130
Head circumference (cm)	101 27.6 ± 1.4	25 26.4 ± 2.0	42 27.5 ± 1.2	34 28.5 ± 1.1

Values given are number in each group, mean ± standard deviation

Of the 104 infants in this analysis, 48 (46.2%) had RDS and 25 (24.0%) required assisted ventilation. Seven infants died before an ultrasound examination of the head could be performed. Of the remaining 97 infants, 54 (55.7%) had any grade of PV-IVH, but only 13 (13.4%) had either grades III or IV PV-IVH.

5.4.2.1 RDS

A significant association between BR and RDS was found (p=0.0042); infants with a greater BR were at higher risk for developing RDS and especially RDS needing ventilatory support

as shown in Table 5.7. There did, however, appear to be differences between males and females. Table 5.7 shows the mean BRs according to whether infants had no RDS, RDS not requiring ventilation or RDS requiring ventilation. While there was a consistent increase in BR for females as RDS severity increased, this was not so for males who had no RDS compared with those with RDS not requiring ventilation. However, for both sexes, those with RDS requiring ventilation had the highest BR (Table 5.7).

Table 5.7 Birthweight ratio of study infants according to sex and occurrence/severity of RDS

	No RDS	RDS not ventilated	RDS ventilated
Females	76.6	81.8	85.5
Males	85.0	79.4	90.7
All infants	81.1	82.1	88.1

Values are expressed as the mean BR (%) in each group where 100% is equal to the 50th percentile

$p = 0.0042$ (analysis of variance)

Using the loglinear model to analyse RDS according to SGA status, a three-way interaction was found ($p<0.03$) between SGA, RDS and sex. On examining the RDS versus SGA data separately by sex, no significant relationship could be found. This was probably due to the small sample sizes available after splitting by sex. However, if the classification of above or below the 25th percentile was used (as opposed to above or below the 10th percentile), females showed a trend towards more severe RDS if they were above the 25th percentile ($p=0.052$) while this did not appear to be so for males ($p=0.18$). When both sexes were combined, this

association was significant (p=0.035) and infants <25th percentile had an odds ratio of 0.31 (95% CI 0.12 - 0.84) of developing RDS needing ventilation vs no RDS when compared with those ≥25th percentile.

RDS was associated with the need for active resuscitation at birth, but not with attendance at antenatal clinic, birthplace (hospital or clinic), mode of delivery, Apgar scores, birthweight or gestation (within the narrow range selected for this analysis).

5.4.2.2 PV-IVH

In the analysis of risk factors for PV-IVH, infants were classified as having no PV-IVH, mild PV-IVH (grades I or II) or moderate-severe PV-IVH (grades III or IV). PV-IVH showed no association with BR or any position in relation to the 10th, 25th or 50th percentiles. Similar to what was reported previously for the larger cohort from which this sample was drawn, infants in this study demonstrated significant associations between PV-IVH and the need for active resuscitation at birth (p=0.026), the need for mechanical ventilation (p=0.032) and the development of pneumothorax (p=0.040). Of the SGA infants, four of 23 had moderate-severe PV-IVH compared with nine of 74 who were appropriately grown. This difference was not significant.

5.4.2.3 Association of RDS and PV-IVH

Table 5.8 shows the interaction of RDS with the severity of PV-IVH. This association did not reach statistical significance for the entire group (p=0.053), but there was a greater than

expected number of infants with moderate-severe PV-IVH amongst infants requiring ventilation for RDS compared with those without RDS (odds ratio 9.67; 95% CI 1.74-53.85) significant at the 1% level.

Table 5.8 Association between RDS and severity of PV-IVH

Grade of PV-IVH	No RDS	RDS not ventilated	RDS ventilated	Total
No PV-IVH	29	9	5	43
Grades I & II	21	9	11	41
Grades III & IV	3	5	5	13
Total	53	23	25	97

Numbers of infants in each category are shown

Chi square = 9.33; p = 0.053

5.4.2.4 Mortality

A total of 32 of the 104 infants died (30.8%). Neither BR nor any category within the percentiles showed a significant association with mortality. Table 5.9 shows the number of infants who died in this study and the causes of death. It can be seen that there was no difference between the proportion of infants above or below the 25th percentile who died nor were there any significant differences as to the causes of death.

Table 5.9 Causes of death according to birthweight category

Cause of Death	Birthweight ≥ 25th percentile (total = 36)	Birthweight < 25th percentile (total = 68)
RDS	5	3
PV-IVH	1	3
Septicaemia - congenital	2	4
Septicaemia - acquired	1	7
Necrotising enterocolitis	1	5
Total deaths (% mortality)	10 (27.8%)	22 (32.4%)

None of the group differences was significant

5.4.3 Discussion

The low birthweight population in this study would appear to differ markedly in its birthweight/gestational age distribution when compared with two recent studies utilising BR. In the study of Brownlee *et al* (1991), the mean BR was close to unity while that of Morley *et al* (1990) showed only a slight negative skewness. In contrast, the infants in this study had a mean BR of 83% with only two infants having a BR >100%. Of the infants in this study who fell below the 10th percentile and were classified as SGA (24% in all), most also had head circumference and length measurements below the 10th percentile, while the mean values for birthweight, length and head circumference were all approximately on the same position between the 10th and 25th percentiles. This suggests that in the majority of these infants the cause(s) of the growth retardation was of relatively long duration (Kliegman and Hulman,

1987). This pattern of symmetrical growth retardation is likely to be prevalent in most parts of the developing world where nutrition and socioeconomic circumstances are poor and differs markedly from the pattern demonstrated by infants who were the subjects of the above studies performed in developed countries utilising the BR.

The effects of this pattern of intrauterine growth on our study population appear to be measurable in the incidence and severity of RDS. It is not clear why this association was more consistent for females than males, but the relatively small numbers in each subgroup may have resulted in some inconsistencies. We speculate that the 'intrauterine stress' experienced by infants with a lower BR induced more rapid maturation of the surfactant system resulting in relative protection against the development of RDS, especially that severe enough to require ventilatory support. This is in keeping with the studies of Gluck and Kulovich (1973) and Procianoy *et al* (1980). Infants ≥25th percentile in this sample had an incidence of RDS of 56% compared with 69% for white infants in Johannesburg who were 30-32 weeks gestation taken from the cohort described in section 5.2. This difference is much smaller than the almost twofold black/white difference found for all infants 29-34 weeks gestation. Thus, the difference between RDS incidence in black and white infants in the Johannesburg area can be explained at least in part by the high incidence of suboptimal intrauterine growth in black infants.

Morley *et al* (1990) reported that SGA infants developed more severe lung disease as evidenced by the requirement for longer periods of mechanical ventilation. Our data did not support this association, but the number of SGA infants requiring mechanical ventilation in our study was small and we could not exclude the possibility that, in those SGA infants

actually requiring ventilation, RDS was more severe. The differences between studies may relate to different populations studied as well as to the causes and duration of intrauterine growth retardation.

This study supports previous data suggesting that the BR allows for a more sensitive analysis of outcome (Brownlee *et al*, 1991). This is probably due to the fact that, since it is a continuous variable, associations involving infants who are suboptimally grown but remain above the 10th percentile can still be demonstrated.

Analysis of the risk factors for PV-IVH in this study failed to reveal an association with any measure of intrauterine growth. Our data are neither in keeping with those of Bada *et al* (1984) or Heinonen *et al* (1985) who showed intrauterine growth retardation to be an added risk factor nor with those of Pena *et al* (1988) and Procianoy *et al* (1980) who suggested a protective effect. The numbers of infants in our study with either grades III or IV PV-IVH were small, but our study did not support the finding that SGA infants were at greater risk for more severe grades of PV-IVH as suggested by Heinonen *et al* (1985). The lack of association with intrauterine growth and the association of PV-IVH with the need for resuscitation at birth, the need for mechanical ventilation and the development of pneumothorax in our study, suggests that PV-IVH in our population is largely determined by events occurring in the immediate perinatal period.

This study showed no clear association between RDS and PV-IVH. Although PV-IVH was associated with mechanical ventilation, it should be noted that a number of infants in our institution are ventilated for reasons other than RDS, e.g. congenital pneumonia, birth asphyxia

and severe apnoea. While a number of studies have shown that preterm infants with RDS are at increased risk for PV-IVH (Goddard-Finegold, 1984; Levene *et al,* 1982; Volpe, 1989a), Philip *et al* (1989) reported a decline in PV-IVH without a concomitant decrease in RDS, while Leviton *et al* (1989) could find little impact on PV-IVH from the literature on prophylactic and rescue trials of surfactant. Apart from the need for active resuscitation at birth, RDS in this study was associated with good intrauterine (i.e. prenatal) growth, while PV-IVH appeared to be associated largely with perinatal events. This would explain the lack of a strong association demonstrated in this study and lends support to the theory that the two conditions may rather be independent indicators of immaturity of organ systems (Leviton *et al*, 1989).

The basis of the conclusions reached above depended on an accurate assessment of gestational age. We, however, did not have the benefit of accurate antenatal gestational age assessments in most cases and therefore relied on postnatal clinical assessments. We attempted to minimise inter-observer variability by only having two observers. However, it has been suggested that both intrauterine growth retardation and race may affect these assessments resulting in an overestimation of gestational age (Ballard *et al,* 1991; Parkin, 1971). If in fact gestation was overestimated in our study, the broad conclusions reached would still be valid with respect to the analyses on BR since it is a continuous variable and does not depend on absolute cutoff values.

The relative protection experienc l by infants in this study with lower BR against RDS may have predicted a more favourabl outcome for them. However, mortality did not differ in our study according to position c : the growth percentiles. Although there were no significant

differences in the causes of death as shown in Table 5.9, the numbers were small There did, however, seem be a trend towards more deaths in those ≥25th percentile from acute RDS, while those <25th percentile seemed to have more deaths from nosocomially acquired infections and necrotising enterocolitis. Van Heel and de Leeuw (1989) showed an increased incidence of gastrointestinal problems and infections in SGA infants, in keeping with the trend shown in our study.

We speculate that, although infants with a lower BR are partially protected against RDS, this does not result in improved neonatal survival due to a trend towards more gastrointestinal and/or infectious complications. The pattern of symmetrical intrauterine growth demonstrated by this population of LBW infants cannot therefore be regarded as conferring any overall advantage, even in the neonatal period. The long term outcome of surviving VLBW infants with IUGR is addressed in the long term follow-up study (Chapter 6)

5.5 Investigation of Early Postnatal Steroids for Infants <1000g at Birth (Shipalana *et al,* 1994)

As discussed in Chapter 4, due to the large numbers of infants requiring assisted ventilation, extremely low birth weight infants weighing less than 1000g at birth were rarely offered mechanical ventilation resulting in a high mortality for this group of infants. In view of the paucity of other studies on non-ventilated VLBW infants and the reported success of early postnatal dexamethasone in ventilated infants in diminishing the ventilatory requirements, it

was decided to conduct a trial on the administration of a course of dexamethasone to non-ventilated infants <1000g.

5.5.1 Methods

Infants with birthweight <1000g who were admitted to the neonatal unit within 12 hours of birth were eligible for enrollment. Standard practice for such infants consisted of routine admission to the high care area where they were nursed in incubators and given oxygen according to their requirements and theophyllin. Antibiotics (penicillin and amikacin) were administered to infants of this birthweight pending the results of the full blood count and blood cultures which were taken soon after birth. Intravenous fluids were given as required and all other appropriate therapy apart from mechanical ventilation was provided as previously described. Since it was felt that steroid therapy would be of no benefit to those infants who died soon after birth, only those who had survived for at least 12 hours were eligible for the study. Gestation was assessed and infants classified by birthweight and gestation as in the previous studies. Those with major congenital abnormalities, signs of infection at birth or those with gestation >32 weeks (i.e. those with severe IUGR) were excluded from the study.

Random numbers were computer-generated in blocks of ten with equal numbers of study and control infants and assignment was made by drawing sealed envelopes. Those infants randomised to the treatment group were given intravenous dexamethasone 0.5mg/kg daily for the first seven days commencing between 12 and 24 hours after birth. Since the control group received no placebo this was not a blinded study. Dexamethasone given to study infants was stopped at any stage if there was a strong clinical suspicion or laboratory confirmation of

infection. Infants in both groups were followed for the duration of their hospital stay.

Chest radiographs were obtained on infants with significant respiratory distress wherever possible. If an infant died of respiratory failure before a chest radiograph could be obtained and there was no laboratory evidence of infection, the infant was assumed to have had RDS. Cranial ultrasound examinations were obtained at least once in the first week of life and then at 14 and 28 days postnatal age. Papile's classification of intraventricular haemorrhage was used (Papile *et al,* 1978).

The potential magnitude of the reduction in mortality from this intervention was unknown and various calculations on sample size were performed. For example, in order to achieve a 30% reduction in mortality (beta value 0.7, alpha value 0.95), it was calculated that 31 steroid treated infants and 31 control infants would be required for the study. Since this number of infants could be enrolled over a period of about one year, this sample size was accepted with the acknowledgement that a beta error could occur. If only a trend was shown, this study could then be regarded as a pilot study for planning of a future larger trial. Comparison between the two groups was done using the Student t or the chi-square test and, where a cell had an expected value of <5, Fisher's exact test was used.

5.5.2 Results

A total of 68 infants with birthweight <1000g were admitted to the unit from February to October 1990. Of these, 25 infants died prior to 12 hours of age, one infant was not enrolled

due to failure to obtain consent and two infants did not meet the inclusion criteria (one fetal alcohol syndrome, one severely growth retarded with a gestation of 33 weeks). A total of 40 infants were thus enrolled over this period. The reason why this was lower than the numbers calculated to show statistical significance was that, during the course of the study, concern was expressed that there appeared to be more deaths in the treatment group. It was therefore decided to perform an interim analysis after 20 infants had been enrolled in each group at which time 15 study infants had died compared with eight control infants ($p=0.055$). Since the trend towards a worse outcome in the treatment group was approaching statistical significance and, based on these data, there was no chance of showing any benefit to the study group by continuing to enrol infants until the original target of 31 in each arm of the study had been reached, it was not felt ethically justified to continue and the study was thus stopped.

Table 5.10 shows details of the infants enrolled. While mean birthweights in the two groups were similar, there was a trend towards lower gestation, fewer infants with IUGR and more males in the steroid treated group. None of these differences, however, reached statistical significance.

Table 5.10 Details of infants enrolled (steroid vs placebo)

	Steroid Group	Control Group
Number enrolled	20	20
Birthweight (g)*	856 ± 98	861 ± 102
Range (g)	675-985	650-990
Gestation (wks)*	27.8 ± 1.1	28.5 ± 1.3
Range (wks)	26-30	27-31
Male/Female (n)	10/10	6/14
SGA/AGA (n)	10/10	15/5

SGA = Small for gestational age

AGA= Appropriate for gestational age

* Mean ± SD

One infant in the study group had a group B streptococcus cultured at birth. This result became available at 72 hours of age at which time the dexamethasone was stopped, but the infant, who survived, was kept in the study group for analysis. No other infants had to be withdrawn from the study. The outcome of the study and control infants in terms of morbidity and mortality can be seen in Table 5.11 There were no significant differences in terms of the occurrence of RDS, PV-IVH, necrotising enterocolitis or nosocomially acquired infections.

Table 5.11 Morbidity and mortality (steroid vs placebo)

	Steroid Group	Control Group
Number enrolled	20	20
RDS (n)	15	16
PV-IVH (n)		
All grades	10	8
Grades III or IV	4	3
Necrotising enterocolitis (n)		
Suspected	2	4
Proven	0	1
Infection (culture proven)(n)		
Congenital	1	0
Nosocomially acquired	5	5
Died (n)	15	8

Electrolytes were measured routinely on the third day of life in all infants and repeated according to clinical indications. None of the infants showed evidence of hyperkalaemia. Sodium, urea and creatinine were transiently elevated in some infants in both groups, but this usually corrected once the volume of intravenous fluids had been increased. Transiently elevated blood sugar levels without glycosuria were noted in a few patients given dexamethasone, but in no case was it of sufficient concern to warrant stopping the dexamethasone or reducing the glucose concentration of the intravenous fluid (routinely 10%). Weight loss in the early days after birth and subsequent weight gain were similar in the two groups.

In view of the trend towards a higher mortality in the steroid treated group, the causes of death were analysed in greater detail. Three infants in each group died within 48 hours of enrollment

from RDS. A further six infants (four study, two control) died of nosocomially acquired infection. Prematurity related causes such as those attributable to the acute or ongoing effects of RDS, PV-IVH or severe apnoea (usually in association with RDS) accounted for the remaining deaths. Further analysis combining both groups revealed a trend towards a lower mortality for females when compared with males (50% vs 69%) and SGA infants when compared with AGA infants (52% vs 67%). Again, however, these differences were not significant.

5.5.3 Discussion

This study showed no benefit of early postnatal administration of dexamethasone for non-ventilated extremely low birthweight infants <1000g in terms of the primary endpoint of this study, namely improved survival. Indeed the study was stopped when a trend towards improved survival of the control group was approaching significance. This study is in keeping with that of Baden *et al* (1972) who could demonstrate no benefits from early postnatal administration of steroids and suggests that the benefits of early postnatal steroids on ventilated infants as demonstrated by Cummings *et al* (1989) and Yeh *et al* (1990) cannot be extrapolated to non-ventilated infants.

A major question raised by our study is whether in fact postnatal administration of dexamethasone may have resulted in an increase in mortality. We analysed data from our unit from October 1989 (when comprehensive computerised record keeping was introduced) to December 1991, excluding the time period during which the study was conducted. A total of

129 infants with birthweight <1000g would have met the inclusion criteria for this study, i.e. survival for more than 12 hours after birth, no congenital abnormalities etc. The mortality over the non-study period was 62.8% compared with the overall mortality of 57.5% seen during the study period. This difference was not significant. Further analysis of infants <1000g admitted in the period immediately before and after the study period revealed that 33.3% had culture-proven nosocomial infections compared with 25% seen in the study infants; again this difference was not significant. Many factors were responsible for the high number of nosocomial infections occurring in our unit and subsequent intervention strategies reduced the magnitude of the problem (Wainer and Gray, 1993). However, there was no evidence from these figures that the use of dexamethasone resulted in an increase in infectious morbidity or overall mortality in this study.

The randomisation process of this study resulted in the control group having more females and infants of greater maturity as evidenced by a higher mean gestational age. While these differences were not statistically significant, it is possible that this imbalance in the randomisation process may have been largely responsible for the adverse mortality trend seen in this study. With the small numbers of infants enrolled in this study, definite conclusions cannot be drawn. Nevertheless the results indicate that postnatal steroid administration without mechanical ventilatory support does not improve the outcome of infants <1000g and therefore cannot be recommended.

5.6 Conclusions

A number of conclusions can be drawn from this series of in-hospital studies. The survival of VLBW infants continues to improve with time and these improvements are due as much to the improvement in general perinatal care as to the benefits and progress of NICU care. The incidence of RDS is lower in black as compared with white infants of comparable gestation in Johannesburg and this appears to be attributable, at least in part, to IUGR which presumably results in increased intrauterine stress. However, the decreased incidence of RDS appears to be counterbalanced by an increase in infection-related complications in infants who are sub-optimally grown in utero resulting in no overall improvement in survival. PV-IVH, on the other hand, appears to be more common amongst VLBW infants at Baragwanath Hospital when compared with published data, but fortunately mainly with respect to grades I and II only. This increased incidence is probably related to the fact that, although perinatal care has improved, it is still sub-optimal. Finally, the use of postnatal steroids on infants with birthweight <1000g at birth did not reduce mortality or morbidity - indeed there was concern that such treatment may be detrimental.

Chapter 6

Long Term Follow-up of VLBW Infants

Preamble

This long term follow-up study was planned and carried out by the author, although as described in Chapter 4, enrollment for the larger Birth to Ten study coincided in time with this study and some of the data collected for that study could be used for comparison. For the first few years of the study, a research nurse was employed to assist with the initial in-hospital data collection and to ensure that follow-up was as complete as possible by maintaining telephonic contact with the families and making home visits when necessary. All data were captured and analysed by the author who was also responsible for preparation of the papers that emanated from this study. This chapter describes follow-up until the age of five years. Longer term follow-up is continuing and, once this cohort of infants has had the opportunity to participate in school activities, further evaluation will be carried out since studies from developed countries have shown that VLBW infants as a group tend to perform less competently at school than do matched infants who were of normal birthweight. However, due to the long term nature of this study, these data will not be included in this thesis.

6.1 Outcome of VLBW Infants at 12 to 18 months of Age
(Cooper and Sandler, 1997)

As discussed in Chapter 2, a review of the outcome of VLBW infants, which included all

English-language publications from 1959 to 1988, revealed that all published studies from which morbidity rates could be calculated had been done in developed countries (Escobar *et al,* 1991), but such data cannot readily be extrapolated due to a number of factors prevailing in developing countries which may have significant effects on later growth and development.

More recently, Thompson *et al* (1993) reported on the outcome of VLBW infants from Cape Town, South Africa, but most of these infants were of mixed race and there was still a paucity of data on the longer-term outcome of surviving black VLBW infants both in South Africa or elsewhere in Africa. This study was therefore initiated to examine the growth and development of surviving VLBW infants discharged from Baragwanath Hospital. Since, apart from a very small number of VLBW infants born in private hospitals, all VLBW infants from Soweto are managed at Baragwanath Hospital, this study could be regarded as a regional rather than a hospital-based sample. As discussed previously, this study was planned with the much larger Birth to Ten (BTT) study in mind (Richter *et al,* 1995; Yach *et al,* 1991), since important socio-demographic baseline data were being collected at that time for all infants born in the Johannesburg area. This section describes the outcome of a cohort of VLBW infants up to 18 months corrected age.

6.1.1 Methods

A stratified sample of infants with birthweight <1500g surviving to hospital discharge representing three predefined subgroups was selected for long term follow-up. These subgroups were:

Group 1: Infants 1000g to 1499g at birth who required mechanical ventilation were consecutively enrolled until 50 infants surviving to hospital discharge had been enrolled. It was estimated that this would take about six months.

Group 2: Infants 1000g to 1499g at birth who did not require mechanical ventilation were enrolled over a 6-week period, corresponding to the enrollment period of the BTT study.

Group 3: Infants <1000g at birth who were not ventilated were consecutively enrolled until 25 infants surviving to hospital discharge had been enrolled. It was estimated that this would take about one year.

Infants were enrolled once they had survived the first 48 hours of life so that gestational age assessments could be performed and to ensure the accuracy of data collection. A number of infants, however, did not survive to hospital discharge, especially those in groups 1 and 3 and enrollment of infants into these groups continued until the target numbers were reached.

An extensive questionnaire was administered to each infant's mother. Details of past medical, obstetric, and family history were obtained, together with information regarding the index pregnancy, smoking, alcohol, and drug use. Details of socioeconomic status were obtained which included the highest educational level obtained by the parents, parental occupation or that of the head of the household, family income, the type of housing, and the presence of running water, electricity, and other amenities in the home. Socioeconomic status was further classified according to a locally validated coding system (Schlemmer and Stopforth, 1979).

All of these data were being collected in the BTT study as outlined in Chapter 4 so that as many determinants of child health and development as possible could be examined.

Details of any complications during labour and delivery, Apgar scores, need for resuscitation at birth, the presence and severity of respiratory distress, infections, and subsequent postnatal complications such as patent ductus arteriosus and necrotising enterocolitis were recorded. In the case of infants requiring mechanical ventilation, additional data such as the oxygenation index at 24 hours of age (Hallman *et al,* 1985), mean airway pressure, development of pneumothorax, need for pressor support, duration of ventilation, and failed extubations were all recorded. Artificial surfactant was not available at that time. Infants in groups 1 and 3 had a transfontanelle real-time ultrasound examination of the head during the first 72 hours of life while all infants had ultrasound examinations at 7-14 days of age using a sector scanner with a 7.5 MHz transducer as described in section 5.3. When PV-IVH or severe periventricular echodensities were noted, ultrasound scans were performed every one to two weeks until hospital discharge. Wherever possible, a further ultrasound examination was done on all infants at four to six weeks of age. The most severe grade of PV-IVH was recorded using the classification of Papile *et al* (1978) and later scans recorded the development of post haemorrhagic hydrocephalus and PVL.

Birthweight was measured by an electronic scale, while head circumference was measured within 72 hours of birth by one of the researchers. Gestational age and the weight for gestation were assessed as described in the previous studies. Weight was subsequently measured twice weekly and head circumference once weekly until hospital discharge. Infants were scheduled for a follow-up appointment six weeks after hospital discharge and then at ages (corrected for

prematurity) three, six and 12 months when growth and developmental status were recorded. Infants who did not return for follow-up visits were actively traced by a research nurse. At the 12-month visit, a full clinical and neurodevelopmental examination was performed, and weight, length, and head circumference were measured. Weight- and length-for-age percentiles were calculated using the Nutritional Anthropometry section of the Epi Info program, which is based on WHO international growth reference curves (Sullivan and Goostein, 1990). Each infant was assessed using the Bayley Scales of Infant Development between 12 and 18 months corrected age (Bayley, 1979). A combined Bayley score of <70 was regarded as indicating handicap while a score of 70 to 84 was regarded as suspect. Hearing screening was performed by testing the response to noisemakers at the follow-up clinic by a speech and hearing therapist. Infants in whom a squint was detected or where there was concern regarding vision were referred for a full ophthalmological evaluation.

Comparisons between subgroups were performed using ANOVA if the data were normally distributed or, if not normally distributed, using the Kruskal-Wallis test. A p value of <0.05 was regarded as significant, and the Bonferroni correction was used when multiple intergroup comparisons were performed. The chi-square and Fisher's exact tests were used when appropriate. To determine predictors of weight and length at one year of age, a multiple regression analysis was performed using weight- and length-for-age percentiles at the one year visit as the dependent variables and anthropometric and clinical data collected during the initial hospital stay as independent variables. A similar regression analysis was performed to examine the predictors of the Bayley scores using socio-demographic, delivery, and postnatal clinical data as independent variables. Both total Bayley scores and the Bayley mental developmental index (MDI) were tested in this way.

6.1.2 Results

In total, 677 infants <1500 g were admitted to the unit during the year in which enrollment into the study was conducted. Table 6.1. shows the total number of infants in the three categories who were admitted to the neonatal unit during the year and the numbers enrolled in each group. Forty-nine ventilated VLBW infants were consecutively enrolled in group 1, 39 non-ventilated infants 1000g to 1499g at birth in group 2, and 25 infants with birthweight <1000g (not ventilated) in group 3. Over the periods of enrollment, only three infants who would have qualified were not enrolled: one mother refused consent for long-term follow-up (group 3), while two infants were missed by the researchers so that important early neonatal data (Ballard scores, head sonars, etc.) were not available (one in group 1 and one in group 3). Of the 113 infants enrolled 90 (79.6%) were born in the hospital, five (4.4%) at a clinic and 18 (15.9%) were born at home but were admitted to the hospital within 12 hours of delivery. Only 38 (33.6%) of the mothers had attended antenatal clinics. Group 1 only had 49 infants instead of the intended 50 as one of the last infants to be enrolled died just before hospital discharge after enrollment of that group was considered complete.

Table 6.1. Details of infants enrolled (long term follow-up)

		Group 1	Group 2	Group 3
Total no. admitted during year		241	325	111
No. of survivors		103	272	27
Percent survival	(95% CI)	42.7 36.4-49.0	83.7 79.7-87.7	24.3 16.6-32.3
No. enrolled		49	39	25
Mean gestation	(wk) (SD)	30.2 1.4	31.3* 1.7	28.6† 1.5
Mean birthweight	(g) (SD)	1255 153	1285 147	872† 90
Mean head circumference	(cm) (SD)	27.4 1.5	27.5 1.4	25.0† 0.9
Birthweight ratio	(%) (SD)	87.3 11.6	81.2 ‡ 11.7	71.5ξ 9.6
AGA/SGA	(n)	41/8	28/11	9/16ξ

* p = 0.005 compared with group 1
† p < 0.0001 compared with the other two groups
‡ p = 0.016 compared with group 1
ξ p < 0.0001 compared with group 1 and p<0.005 compared with group 2

CI = confidence interval
AGA = appropriate for gestational age
SGA = small for gestational age

The mean gestational age, birthweight, and head circumference measurements of the three groups can also be seen in Table 6.1. Although there were no differences in mean birthweight and head circumference between groups 1 and 2, group 1 infants had a significantly lower gestational age than those in group 2. As expected, group 3 infants had a significantly lower mean gestational age, birthweight and head circumference, and the majority of infants in this group were SGA (Table 6.1). Infants in group 1 required mechanical ventilation for a mean

of 11.7 days (range 1-60 days), while total hospital stay for the study infants averaged 50.3 days (range 21-158 days) for those with a birthweight of 1000g to 1499 g and 72.1 days (range 54-107 days) for those <1000g. Only eight infants were discharged from hospital later than term corrected age (four in group 1, one in group 2 and three in group 3) and there were no intergroup differences at the age of discharge.

A total of 58% of the families lived in an apartment or house, while the remainder lived in a shack or some other form of informal accommodation. Electricity was present in 70% of the homes; only 17% of homes had running hot and cold water while an additional 79% had access only to running cold water either inside or outside the home, 29% had a toilet inside the home, and the same proportion had a telephone in the home. The median household income was R600 (1 US$ = approximately 3 SA Rand in 1990), while median parental education was seven years of schooling for the mother and eight years for the father. Only 4% of mothers said they had ever smoked, 89% said they never took alcohol, while only 4% admitted to taking alcohol once a week or more. None of the mothers admitted to taking recreational drugs. All infants in this study were black except one, who was of mixed race.

Fifteen infants died during the first year of follow-up, while 12 others were lost to follow-up. No intergroup differences were found in the numbers of infants who died or who were lost to follow-up (Table 6.2). Mortality was not affected by whether infants had been born in the hospital or at home. Of the infants who died, six deaths were associated with pneumonia and/or septicaemia on subsequent admissions to hospital. Two other infants were admitted to the hospital and died of complications associated with severe protein energy malnutrition and four died at home with a history compatible with a diagnosis of sudden infant death syndrome.

Death was associated with severe growth failure and developmental delay due to fetal alcohol syndrome in one infant, while the cause of death was unknown in two additional infants. Of those who died, three had PVL/porencephaly identified on cranial ultrasound prior to hospital discharge (two in group 1 and one in group 3). Of the infants lost to follow-up, none had PVL/porencephaly identified on cranial ultrasound examinations and only one had a PV-IVH larger than grade II (grade III), which resolved without sequelae on follow-up sonars performed in the hospital.

Table 6.2 Number of infants who died or were lost to follow-up

	Group 1	Group 2	Group 3
Number enrolled	49	39	25
Died after discharge	7	5	3
Percent mortality (95% CI)	14.3 (4.5-24.1)	12.8 (2.3-23.3)	12 (2.5-31.2)
Lost to follow-up	6	4	2
Followed to 1 yr	36	30	20

6.1.2.1 Growth Data

Since a number of infants did not keep scheduled appointments and needed to be traced, the mean ages at which they were seen corresponded to 0.9, 3.4, 7.6, and 13.1 months corrected age, and not all infants were seen at each time period. The mean weight- and length-for-age

percentiles over this period can be seen in Table 6.3. No differences were noted between groups 1 and 2 for weight or length at any age, but group 3 infants were significantly lighter than group 2 infants at a month of age and significantly shorter up to eight months when compared with the other two groups. There were no longer any significant differences at 13 months of age. Head circumference measurements of group 3 infants were significantly lower than those of the other groups at one month of age but did not differ significantly thereafter (Table 6.3). Of note was that length measurements (expressed as length-for-age percentiles) were significantly lower on the percentiles than weight measurements for all groups (expressed as weight-for-age percentiles) at every time period up to 13 months of age.

Table 6.3 Details of growth parameters at follow-up (corrected age)

	Group 1	Group 2	Group 3
Mean 0.9 mo. (range 0.1-2.0)			
WAP	12.6 ± 13.1	16.2 ± 15.7	4.5 ± 4.6 †
LAP	9.5 ± 11.0	15.1 ± 19.0	1.7 ± 2.2 ‡
Head circumference (cm)	36.5 ± 1.8	36.1 ± 1.1	34.8 ± 0.9 ‡
Mean 3.4 mo. (range 2.1-5.0)			
WAP	34.5 ± 26.3	40.8 ± 30.6	20.2 ± 15.6
LAP	16.9 ± 16.4	21.1 ± 21.3	3.9 ± 4.6‡
Head circumference (cm)	40.8 ± 2.1	40.0 ± 1.9	39.6 ± 2.4
Mean 7.6 mo. (range 5.1-10.0)			
WAP	28.1 ± 28.8	24.4 ± 28.9	16.1 ± 14.3
LAP	22.9 ± 24.3	15.7 ± 19.8	4.4 ± 4.6‡
Head circumference (cm)	43.8 ± 2.3	44.1 ± 1.4	43.4 ± 1.7
Mean 13.1 mo. (range 10.1-15.0)			
WAP	21.7 ± 26.0	24.4 ± 23.1	11.3 ± 13.3
LAP	19.3 ± 20.0	14.0 ± 15.3	6.8 ± 7.9
Head circumference (cm)	46.6 ± 2.0	46.3 ± 1.6	45.3 ± 1.9

* Comparisons were performed using Kruskal-Wallis one-way analysis of variance using the Bonferroni correction for all two-way comparisons (ie, $P<0.0167$ regarded as significant). Not all infants were seen at each time period and corrected ages were used throughout.

† Significantly different from group 2.

‡ Significantly different from other two groups.

WAP = weight-for-age percentile (mean ± SD)

LAP = length-for-age percentile(mean ± SD)

Mo. = months

In the multiple linear regression analysis for predictors of both weight- and length-for-age at 13 months, the only significant variable was the rate of increase in head circumference from

the time that birthweight was regained until a weight of 1900g was reached. Weight increase was also significant in the univariate analysis, but was no longer significant in the multivariate analysis. Other variables such as birthweight, gestation, BR, time to regain birthweight, etc. showed no association. There was also no association with the length of time that breastfeeding was continued after hospital discharge or the age at which foods other than milk were introduced.

6.1.2.2 Neurodevelopmental Outcome

Cerebral palsy was diagnosed in nine infants (eight from group 1) while severe truncal and lower limb hypotonia was noted in two other infants (Table 6.4). Both of the latter infants had been abandoned by their mothers and had to be institutionalized. One additional infant with birthweight 700g, who also had features of fetal alcohol syndrome, developed severe ROP and was blind. No other infants were diagnosed as having ROP. Severe hearing loss was not diagnosed in any infant, but testing in some of the infants was inconclusive, especially when it was done at a relatively young age. Of the nine infants with cerebral palsy, six also had Bayley scores <70, while both severely hypotonic infants and the infant with retinopathy also had scores <70. A further three infants without signs of cerebral palsy, all from group 1, had Bayley scores <70. These data are summarised in Table 6.4.

Table 6.4 Details of handicap

	Group 1	Group 2	Group 3
Followed to 1 yr	36	30	20
Cerebral palsy (CP)	8*	0	1
Severe hypotonia	1	1	0
Bayley score <70	9†	1	1
With CP/hypotonia	6	1	0
No CP/hypotonia	3	0	1‡
Total with handicap (CP or Bayley <70)	12*	1	2
Percent handicap (95% CI)	33.3 (17.9-48.7)	3.3 (0.1-17.3)	10 (1.2-31.7)

* p = .006 compared with group 2
† p = .015 compared with group 2
‡ This infant also had severe retinopathy of prematurity and features of fetal alcohol syndrome.

The mean total Bayley, Bayley MDI and psychomotor development index (PDI) scores for the three groups are shown in Table 6.5. Group 1 infants had the lowest mean values, but the differences were not significant for the comparison of the total Bayley and Bayley MDI scores. While analysis of variance showed a significant difference for the Bayley PDI scores (p=0.032), the individual comparisons of group 1 with group 2 (p=0.019) and group 1 with group 3 (p=0.046) were not significantly different once the Bonferroni correction was applied.

Table 6.5 Bayley scores at 12 to 18 months corrected age

	Group 1	Group 2	Group 3
Total Bayley score	83.7 ± 20.3	93.7 ± 12.1	95.0 ± 15.2
Bayley MDI	86.9 ± 23.1	95.5 ± 16.7	98.9 ± 18.1
Bayley PDI*	80.9 ± 20.0	92.3 ± 12.5	91.7 ± 15.6
* Analysis of variance was significant (p =0.032), but individual group comparisons of group 1 with group 2 (p = 0.019) and group 3 (p = 0.046) were not significant when the Bonferroni correction was applied			

6.1.2.3 Predictors of Neurodevelopmental Handicap

Of the nine infants diagnosed with cerebral palsy, eight had PVL and/or porencephaly diagnosed on serial ultrasound examinations during their initial hospital stay. Of these, three infants had grade IV PV-IVH with subsequent post-hemorrhagic hydrocephalus and large areas of porencephaly, one of whom required a ventriculo-peritoneal shunt; two infants had grade III PV-IVH with subsequent post haemorrhagic hydrocephalus and PVL and both required ventriculo-peritoneal shunts, and three infants had grade II PV-IVH but subsequently developed severe PVL. The remaining infant had a small grade II PV-IVH, which resolved, and no PVL was detected at the time of the last ultrasound examination at 29 days of age. Of those infants without cerebral palsy at follow-up, only two had a PV-IVH larger than grade II (both grade III), which resolved without sequelae, while one other infant had a grade II PV-IVH and later developed a single anterior 1 cm cyst in the periventricular white matter. No other infants without cerebral palsy at the 1-year follow-up demonstrated PVL and/or

porencephaly on ultrasound. Thus, the finding of PVL/porencephaly on cranial ultrasound during the initial hospital stay had a sensitivity of 89% and a specificity of 99% for predicting cerebral palsy as diagnosed at one year of age.

Using multiple linear regression analysis, the strongest negative predictor of developmental status as measured by the total Bayley scores or the Bayley MDI was the development of cystic PVL or porencephaly during the initial hospitalization of this group of VLBW infants. Other factors significantly associated with a higher Bayley score for the entire group were higher maternal educational level, the adequacy of intrauterine growth as measured by either a higher birthweight ratio or a higher categorical weight classification and fewer total days in supplemental oxygen. None of the many other factors that were analysed such as socio-demographic markers, pregnancy-related complications, the many clinical complications in the neonatal period, or growth in hospital (weight gain and increase in head circumference) showed any significant association with Bayley scores. Measurements of weight, length, and head circumference after hospital discharge were also not significantly associated with the Bayley scores.

Since this was a stratified sample drawn from infants admitted to the unit over a one year period, it was necessary to use the total survivors in each group over the entire 1-year period in order to determine expected handicap rates at our institution for all infants with birthweights <1500g. Figure 6.1 summarises the expected outcome at 12 to 18 months of age of VLBW infants at our institution surviving to hospital discharge when the rates found in this study are applied to all VLBW survivors during the year of study.

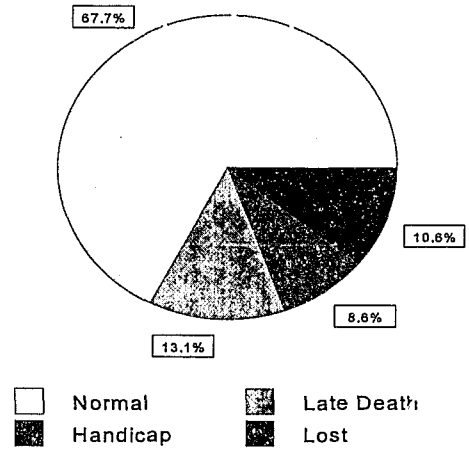


Figure 6.1 Expected outcome at 12 to 18 months of age of infants <1500g surviving to hospital discharge based on data from this study

6.1.3 Discussion

The infant mortality rate for blacks in the Johannesburg-Soweto area was previously estimated to be <30/1000 (Yach, 1988), although informal settlements and squatter areas were excluded in this survey. The true figure was thus somewhat higher. The Province of Gauteng, which includes Johannesburg, was estimated to have a black infant mortality rate of 43 in 1990, while the estimate for the country was 52/1000 live births (Bellamy, 1996; Chimere-Dan, 1995). This compared with 7/1000 for industrialised countries (Bellamy, 1996). Of the original 113 infants enrolled in this study, 15 were known to have died after hospital discharge, giving a mortality between hospital discharge and one year of age of >130/1000 for this sample of infants. VLBW infants in our area, in addition to having high a neonatal mortality, were thus at much greater risk of dying between hospital discharge and one year of age when compared

with infants of normal birthweight.

The main causes of death related to serious infections in the early months after hospital discharge and probable sudden infant death syndrome. This appears to be a high rate of sudden infant death syndrome, but the diagnosis was made on history alone and, because no postmortem examinations were done in these cases, other factors may have been responsible for the deaths. No deaths were associated with severe bronchopulmonary dysplasia. PVL was diagnosed by cranial ultrasound in hospital in three of the 15 infants who died, not significantly different compared with eight of the 86 survivors. In addition, deaths occurred in the same proportion in all three subgroups followed up. Thus the high mortality could not be related directly to complications suffered in the neonatal period. However, the numbers of infants with bronchopulmonary dysplasia and/or PVL may have been too small to show such an association.

The BTT study, which was taking place concurrent with this study, suggested that the families of VLBW infants came from poorer socioeconomic conditions. For example, 42% lived in informal housing compared with 23% in the overall BTT study, average education of parents of VLBW infants was one year less, and family income in the case of VLBW infants was approximately 60% of the average income found in the overall BTT study (Dr T. de Wet, personal communication). Thus, the high mortality after hospital discharge in this group reflects, at least in part, the extremely poor socioeconomic conditions of these families.

The mean BRs in this study ranged from 87.3% in group 1 to 71.5% in group 3, reflecting a high incidence of suboptimal intrauterine growth. The highest BR was seen in group 1 infants

who also had the lowest number of SGA infants. It was shown in section 5.4 that better intrauterine growth is associated with a higher incidence of RDS in our population and it would thus be expected that VLBW infants requiring ventilation would have a higher BR. Since infants <1000 g at our institution were not usually ventilated, it is not surprising that the majority of those who survived were SGA.

There appeared to be some catch up growth in the first three to four months after hospital discharge, but mean weights subsequently declined on the percentiles so that, at 13 months of age, the mean weights were between the 10th and 25th percentiles. Infants in group 3, the majority of whom were SGA, did appear to demonstrate some catch up growth in relation to the other two groups in that, at one year of age, there were no longer any significant anthropometric differences between the groups. Head circumference measurements were close to the 50th percentile for all groups from three months corrected age onwards.

The only significant factor associated with weight and length at one year of age was the rate of increase in head circumference during the initial in-hospital stay, which in turn was probably the earliest reflection of the growth potential of these infants in an extrauterine environment. The fact that, throughout the first year of life, the weight of the study infants was significantly higher on the percentiles than the length suggests that postnatal nutrition was not a limiting factor for growth of these infants as a group, though this may have been a factor in isolated cases.

Thus it would seem that this group of infants, coming from extremely poor socioeconomic circumstances and generally suboptimally grown at birth, remained relatively small up to one

year of age, especially in terms of length. However, the pattern of postnatal growth demonstrated by this group of VLBW infants is analogous to recent studies reported from developed countries. These studies have generally shown VLBW survivors to be smaller as a group than infants with normal birthweight, especially in those VLBW infants who were SGA at birth (Casey *et al,* 1990; Hack *et al,* 1984; Karniski *et al,* 1987; Kimble *et al,* 1982).

6.1.3.1 Neurodevelopmental Outcome

In this study, nine (10.5%) of the 86 infants followed were diagnosed as having cerebral palsy at one year of age. If the rates found in the three groups in our cohort are representative of all infants <1500g discharged during the year, the majority of whom were 1000g to 1499g and did not requiring ventilation, the expected rate of cerebral palsy would be 5.9% for those surviving to one year of age. This compares with the meta-analysis of Escobar *et al* (1991) who showed a median cerebral palsy rate for VLBW survivors of 7.7% (95% CI 5.3 to 9.0), and is also similar to rates shown in other recent studies from developed countries (Cooke, 1990; Cummins *et al,* 1993; Robertson, 1994; Veen *et al,* 1991). It is notable that handicap rates in these studies were similar for those with birthweight 1000g to 1499g and those <1000g, and handicap rates also did not differ over time. The high sensitivity and specificity of PVL/porencephaly for the prediction of later cerebral palsy are in agreement with other studies showing PVL/porencephaly diagnosed on cranial ultrasound to be the best predictor of later cerebral palsy (Hansen *et al,* 1989; Pidcock *et al,* 1990; Pinto-Martin *et al,* 1995; Rogers *et al,* 1994). Of the 12 infants lost to follow-up, none had PVL/porencephaly demonstrated on cranial ultrasound, which suggests that the cerebral palsy rates as calculated above are unlikely

to have been higher and may in fact have been lower had there been no losses to follow-up. PVL/porencephaly diagnosed on cranial ultrasound was also the strongest predictor of the Bayley scores at 12 to 18 months of age.

Although, we previously showed an association between socioeconomic status and long term developmental outcome in white VLBW infants (Cooper *et al,* 1989), we were unable to show an association in this study between outcome and socioeconomic status using occupational class, income, or any other measures such as quality of housing, conveniences in the home, etc. It is probable that, in a situation such as ours in a typically third-world urban community, the spectrum of socioeconomic status is too narrow to show this association. Maternal education in our study, however, was a predictor of later developmental outcome and is probably a proxy measurement of some of the factors determining socioeconomic status in developed countries.

It was shown in section 5.4 that a lower BR at our institution is associated with a lower incidence of RDS, but that overall survival was no better than those with a higher BR due to the development of other complications, especially infections. An important finding of this study was that poorer intrauterine growth was associated with lower developmental scores at 12 to 18 months of age. Although most infants with major handicap were from group 1, who had the highest mean BR, this association was nevertheless significant, suggesting that the long term effects of suboptimal intrauterine growth are more subtle. Thus, while suboptimal intrauterine growth may be associated with a short-term advantage in our population of VLBW infants in the form of less RDS, the longer-term disadvantages would appear to outweigh the advantages and optimal intrauterine growth should be the goal.

For infants 1000g to 1499g at birth, the need for mechanical ventilation was associated with an increased risk of handicap (cerebral palsy alone or combined with Bayley score <70), while non-ventilated infants generally had a very good outcome. The association of Bayley scores and the total time in oxygen for the whole cohort is further evidence that later outcome is related to severity of illness in the early neonatal period, especially when assisted ventilation is required. Only one of 20 infants <1000g at birth followed to one year had cerebral palsy while an additional infant had severe ROP and had a Bayley score <70. The high mortality of infants in this weight category at our institution appears to be associated with handicap rates that are relatively low.

It should be emphasised that infants diagnosed as having cerebral palsy at one year of age may 'outgrow' this condition while other milder cases of cerebral palsy may be missed at one year of age (Nelson and Ellenburg, 1982). Nevertheless, developmental assessment at one year has been shown to correlate well with later outcome (Ross *et al,* 1986). In spite of many differences in population characteristics, tertiary care facilities, and survival figures when compared with VLBW infants in developed countries, the rates of handicap and general outcome measures in this cohort of VLBW infants seem broadly comparable with recent figures from developed countries.

6.2 Growth and Development of VLBW Infants Up to Age Five Years

Following the developmental tests that were performed on this cohort of VLBW infants

between 12 and 18 months of age, a further visit was scheduled at a corrected age of two years and then subsequently once per year. However, it was noted that there was great geographical mobility of these families as well as changes in the main care-givers of the infants. Those mothers who were in some form of employment frequently arranged that another adult female member of the family would care for the infant. In most cases this was the infant's maternal grandmother. Where the new care-giver was also living in the Johannesburg/Soweto area, follow-up was relatively easy, but in many cases the care-giver lived elsewhere, frequently in a rural area, and follow-up in these cases was not as straightforward. In addition, the years between 1991 and 1994 saw a great deal of political violence in South Africa and it was often not clear at the time who was instigating the violence. Thus it became dangerous for the nursing sister involved with the tracing of the infants who failed to return to follow-up to go into areas where she was not known asking as to the whereabouts of the family. The result was that the numbers of infants who were seen each year became fewer due to an ongoing 'drop out' from the study and, in addition, one infant from group 1 who had severe quadriplegia and mental retardation subsequently died. Table 6.6 shows the numbers of infants seen at various time intervals up to age five years classified according to the original subgroups.

Table 6.6 Numbers of infants followed up to age five years

	Group 1	Group 2	Group 3	All*
Enrolled	49	39	25	100%
1 Year	36	30	20	88%
3 Years	27	26	11	66%
5 Years	20	23	13	58%

* Expressed as a % of those known to be alive (15 deaths in the first year and one subsequently).

6.2.1 Growth to Age Five Years

The mean weight and length/height percentiles between one and five years of age are shown in Table 6.7. It can be seen that the mean weight-for-age percentile did not change between one and three years of age but, by the age of five years, the mean weight-for-age percentile had fallen significantly from the 19th percentile at one year to the 13th percentile at five years ($p=0.016$). In contrast the mean length/height-for-age percentile increased significantly from the 14th percentile at the age of one year to the 19th percentile at three years of age ($p=0.007$) and then to the 25th percentile at five years of age ($p=0.0006$). Mean head circumference measurements (not shown in Table 6.7) were already close to the 50th percentile at one year of age and remained there up to five years of age with no intergroup differences.

Table 6.7 Mean weight and length/height percentiles (all groups combined)

	Weight-for-Age (Mean percentile ± SD)	Length/Height-for-Age (Mean percentile ± SD)
1 year	19.2 ± 22.6	14.4 ± 16.8
3 years	17.8 ± 19.6	18.8 ± 20.5 #
5 years	13.4 ± 19.7 *	24.8 ± 27.0 ##

* p = 0.016 Compared with 1 year percentile

\# p = 0.007 Compared with 1 year percentile

\## p = 0.006 Compared with 1 year percentile

Similar to the multiple linear regression analysis at one year of age for predictors of weight- and length/height-for-age, the only significant predictor at five years was the rate of increase in head circumference from the time that birthweight was regained until a weight of 1900g was reached prior to the first hospital discharge. Variables such as the birthweight, gestation, BR, time to regain birthweight and early post-discharge growth and feeding practices showed no association.

6.2.2 Neurological Follow-up

Cerebral palsy was diagnosed in nine infants at the one year follow-up (Cooper and Sandler, 1997). Of these, one infant subsequently died as mentioned above. Of the remainder, all were regarded as still having cerebral palsy at five years of age. Three were assessed as having mild handicap at the age of five years and five had a major handicap according to the classification described by Veen *et al* (1991). Two infants thought to be normal at one year were

subsequently diagnosed as having mild cerebral paisy of the diplegic type with slight shortening of the Achilles tendon and a mild increase in flexor tone at the ankles (unilateral in the case of one infant). However, neither had significant handicap (one was minimally impaired and one had mild disability) and, by five years of age one of them was considered once again to have a normal neurological examination. Neither of these infants were noted to have post haemorrhagic hydrocephalus, PVL or porencephaly on head sonars performed during their initial hospital stay.

6.2.3 Discussion

Long term follow-up of this group of VLBW infants proved to be difficult in the face of poor socioeconomic conditions, great individual mobility and political unrest with the result that just less than 60% were followed to five years of age. Such difficulties are likely to be common in many developing country settings. However, since there did not appear to be significant differences between those who were lost to follow-up and those who were seen, it is probable that the results of this five year follow up can be extrapolated to the whole cohort.

The growth data indicate that catch up growth as regards length/height continued through the early childhood years in this group of VLBW infants. This occurred in spite of the fact that the average weight-for-age decreased significantly. The latter would suggest that nutrition during these years was not optimal and the reasons for the increase in length/height are not clear. Catch up in stature has been described previously in VLBW infants, but this has usually occurred in the first two years of life (Hack *et al*, 1984). Data on later catch up growth of VLBW infants is conflicting with some studies showing no catch up between two and five

years of age (Kitchen *et al*, 1989), while others have shown catch up growth occurring up to and into adolescence (Hirata and Bosque, 1998). It may be that, at least in some of the infants in this study, many of whom were growth retarded at birth, the steady increase in stature over the study period was a reflection of their genetic potential. Unfortunately, parental height was not recorded and could therefore not be used for analysis. As was reported in the follow-up of these infants at one year of age, the rate of increase in head circumference during the initial in-hospital stay remained the best predictor of later growth performance and may perhaps be the earliest indicator of this genetic potential. Further studies will be needed to confirm this association.

With respect to neurological outcome, no infants who had been diagnosed as having cerebral palsy 'outgrew' this condition by five years of age, while two further infants had subsequent signs of neurological abnormality which were missed at one year of age. In neither case, however, were these abnormalities of major clinical significance and indeed one of these children appeared to outgrow these abnormalities later on. Thus, as with other studies, neurological assessment at one year of age correlated well with later outcome. The initial follow-up (Cooper and Sandler, 1997), showed that the diagnosis on cranial ultrasound of PVL and/or porencephaly during the neonatal period predicted cerebral palsy as diagnosed at one year of age with a sensitivity of 89% and a specificity of 99%. This remained true in our cohort for predicting cerebral palsy associated with significant handicap at five years of age.

6.3 Conclusions

This long term follow-up study has shown that surviving black VLBW infants in Johannesburg have a rate of cerebral palsy similar to the rates described in the literature which originate mainly from industrialised countries. Cerebral palsy could largely be predicted on the basis of serial cranial ultrasound examinations performed prior to the initial hospital discharge of these infants and occurred predominantly in those who required assisted ventilation in the immediate neonatal period. The Bayley MDI scores correlated with ultrasound findings and the level of illness, but also correlated with the adequacy of intrauterine growth. Taken together with the conclusions at the end of the previous chapter, sub-optimal intrauterine growth is clearly detrimental for VLBW infants. The neurological evaluations of these infants at one year of age correlated well with those at five years of age. Weight and height at follow-up were predicted best by the rate of increase in head circumference during the initial hospital stay. Although these infants remained relatively small as a group up to the age of five years, ongoing catch up in height was still taking place.

Chapter 7

Conclusions and Ethical Dilemmas

Preamble

This chapter discusses further some of the general conclusions from this series of studies. However, as indicated in Chapter 1, progress in the care of VLBW has elicited numerous ethical debates as new frontiers have been reached. In terms of the published literature, these debates have taken place almost entirely in the context of industrialised countries and the paradigms within which the issues are discussed are frequently not applicable to the situation in developing countries. In the light of the findings of this series of studies, the place of neonatal intensive care in developing countries is discussed in relation to generally accepted ethical principles and certain tentative conclusions are reached. Colleagues in the field of ethics and philosophy have suggested to this author that the discussion presented in this thesis needs to be developed further in order to reach valid ethical and philosophical conclusions. However, the arguments that have been developed are from the perspective of the author as a clinician having to make such decisions, as do many of his colleagues, largely without the benefit of a framework of public policy and with little assistance from ethicists. It is accepted that the arguments put forward need to be developed further and it is suggested that this discussion should be seen as a basis from which this can be done.

This series of studies on low birthweight and VLBW infants at Baragwanath Hospital has resulted in a more comprehensive understanding of the problems experienced by these infants,

how some of these problems differ from those experienced by such infants in developed countries and, in particular, the interaction of IUGR with some of the biological complications experienced by VLBW infants in this population.

7.1 The Profile of VLBW Infants in Johannesburg

Improvements in survival for VLBW infants at Baragwanath Hospital have been dramatic over the last 50 years. This has occurred as a result of major advances in the general care of these infants as well as the introduction of intensive care facilities. Such improvements are likely to be ongoing, but with the negative results of the postnatal steroid study, the improvements in outcome for VLBW infants with birthweight less than 1000g may reach a ceiling until such time as it becomes possible to provide them with ventilatory assistance.

The incidence of very low birthweight in the black population in South Africa is clearly substantially higher than that of most populations in developed countries and that of the white population of South Africa. As illustrated in Chapter 1, figures from the Johannesburg Medical Officer of Health gave a low birthweight rate for whites of 8.6% compared with 16.4% for blacks (Annual Report, 1988). The increasing proportion of VLBW infants at Baragwanath Hospital during the 1990s is probably explained, at least in part, by changes in the utilisation of the hospital by the population. However, over this period of time, the prevalence of human immunodeficiency virus (HIV) positivity amongst the antenatal population increased from 1.5% in 1990 to 14.5% in 1996 (Dr J.A. McIntyre, personal communication) and it is possible that this may also have resulted in an increase in the

numbers of VLBW infants. However, there was no direct correlation between maternal HIV positivity and the incidence of VLBW infants over these years and the extent to which maternal HIV positivity contributes to the incidence of VLBW is not well understood. Nevertheless, 2-2.5% of all deliveries in the Baragwanath delivery network are of infants with a birthweight less than 1500g (at least double that of most populations in the developed world) and, while it is well recognised that different populations have differing frequencies of VLBW, it is still not clear whether this can all be explained by environmental factors. Black mothers in the United States also have a frequency of VLBW of 2-2.5% (McCormick, 1985), a figure which does not appear to have changed over the past half century (McCormick, 1994) in spite of significant improvements in socioeconomic conditions and health care. A recent study by David and Collins (1997) comparing the birthweight of infants born to African-American mothers in the United States with infants born to black mothers delivering infants in the United States but who were themselves born in Africa showed differences in the mean birthweight as well as the incidence of low birthweight with the latter having figures closer to that of white mothers in the United States. However, there was no significant difference in the incidence of VLBW infants in the two populations of black mothers with those of African birth having an incidence of 2.3% which was similar to the figure for African-American mothers of 2.5%, supporting the suggestion that the causes of VLBW may differ from those resulting in larger low birthweight infants (Wilcox and Russell, 1983). It is noteworthy that the frequency of VLBW infants is similar in black mothers in South Africa, those originating in other parts of Africa and residing in the United States, and those born in the United States.

It is also clear that a large proportion of black VLBW infants born in South Africa (over 50% in these studies) are SGA and that the majority of these have head circumference and length

measurements that are also below the 10th percentile of Lubchenco's norms. As previously discussed, this suggests that the cause(s) of their growth retardation is/are of a relatively long duration and it is also possible that these factors may in turn be responsible for the premature delivery that occurs in these infants. This series of studies gives greater insight into the potential advantages and disadvantages of this pattern of IUGR. The major advantage demonstrated by these infants is that they are relatively protected against the development of RDS and consequently less likely to require ventilatory support than white infants of similar gestational age. However, the short term mortality of SGA infants is no better than their peers who are better grown at birth due to the fact that they appear to be more susceptible to infection-related complications and necrotising enterocolitis. In the longer term, the developmental scores of infants in our study were poorer if they had a lower BR at birth. While this was true up to the age of 18 months, it remains to be seen whether this association will still be present as these children get older. Nevertheless, there is no short term survival advantage for these infants and there is evidence that their long term development may be adversely affected; therefore, this pattern of intrauterine growth appears to be undesirable. Unfortunately, however, without knowing more about the causes of this pattern of growth, it will be difficult to develop programmes to reduce the numbers of such infants born. Paradoxically, if the predicted improvement in intrauterine growth occurs as socioeconomic conditions improve, the need for ventilatory support for black VLBW infants may increase.

7.2 Handicap Rates of VLBW Infants in Johannesburg

IUGR in this population of VLBW infants did not appear to be associated with the more severe

forms of PV-IVH or with the development of PVL, which were in turn strongly associated with the development of cerebral palsy. These complications, which usually become ident in the neonatal period, appeared to be associated rather with events that occurred during the perinatal period, such as perinatal asphyxia as evidenced by the need for resuscitation at birth and the development of pneumothorax, rather than events which appeared to have their origin in earlier gestation. Although it was encouraging to note that the rate of major handicap in general and cerebral palsy in particular was similar to that in most other parts of the world and particularly that in developed countries, a closer examination of the data on the infants in group 1 in our long term follow-up study, i.e. those who required ventilatory support in the neonatal period, gives less cause for optimism. It was noted that, during 1990, only 43% of infants with a birthweight 1000-1499g in whom ventilation was initiated survived. Of those 49 infants in this study who were ventilated and survived to hospital discharge, a further seven died during the first year of life after hospital discharge and six were lost to follow up. Of the 36 infants in this group who were followed to 18 months, 12 were regarded as handicapped as described in Chapter 5. Thus only 21% of this group of infants in whom mechanical ventilation was initiated were known to be normal survivors at a corrected age of 12-18 months. No infants who were lost to follow-up were noted to have either intraparenchymal bleeding or developed PVL, the major predictors of later handicap in this study and those of others (Hansen *et al,* 1989; Pidcock *et al,* 1990; Pinto-Martin *et al,* 1995; Rogers *et al*, 1994). If it was assumed that all of those lost to follow-up were also normal at this age, then still only 26% of this group were normal at 12-18 months of age. The outcome of all infants 1000-1499g at birth in whom ventilation was initiated can be seen in Figure 7.1.

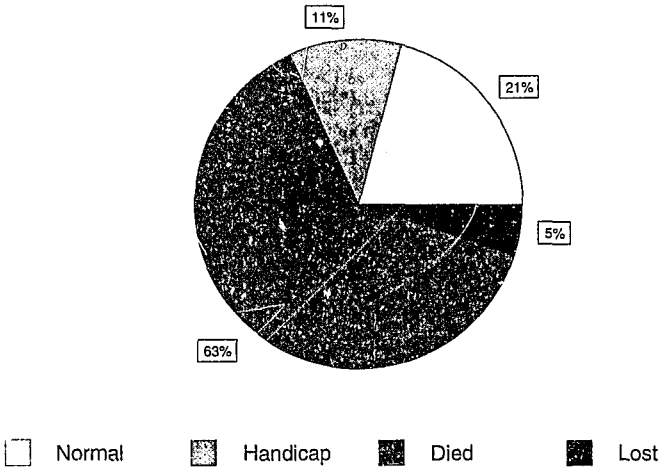


Figure 7.1: Overall outcome at age 12 to 18 months of infants with birthweight 1000-1500g who required mechanical ventilation after birth

However, even as these figures are analysed, as has been the case in other parts of the world, by the time longer term outcome data on VLBW infants become available, the intervening years have seen significant changes in the care and short term survival of these infants, making the direct application of long term follow up results difficult. In the case of VLBW infants at Baragwanath Hospital, survival over the five-year period from 1990/91 to 1995/96 improved substantially, especially in those with birthweight 800 to 1299g where the improvement in survival was in the order of 10-15%. Furthermore, with the introduction of free health care for pregnant women, the average time of first attendance at antenatal clinics has changed from 29 weeks of gestation to 24 weeks and there has also been a substantial increase in the use of antenatal steroids (Dr E. Buchman, personal communication). Thus there has already been an improvement in short term survival of VLBW infants and some of the factors related to suboptimal care in the ante- and perinatal periods that are associated with large PV-IVH and

PVL have also been affected favourably. Thus it is possible that the number of intact survivors in the group of VLBW infants requiring assisted ventilation may also be increasing. These studies have confirmed the work of others that major handicap at 12-18 months of age is strongly associated with the development of PVL or porencephaly during the initial hospital stay (Hansen *et al,* 1989; Pidcock *et al,* 1990; Pinto-Martin *et al,* 1995; Rogers *et al,* 1994). Thus an in-hospital study at this stage including pre-discharge cranial ultrasound examination should give a strong indication as to whether the numbers of intact survivors, especially in ventilated VLBW infants, are increasing. Such a study is currently being planned.

On the other hand, the long term outcome of VLBW infants who did not require intensive care was remarkably good. In those with birthweight 1000-1499g, no infants were diagnosed as having cerebral palsy while only one such infant with birthweight <1000g had cerebral palsy. Two additional infants were handicapped, but there were contributing factors in both cases: one had been institutionalised after hospital discharge while the other was diagnosed as having fetal alcohol syndrome and also developed severe retinopathy of prematurity. Thus in comparison with the outcome of surviving VLBW infants in the era that preceded modern neonatal intensive care, VLBW infants who did not require the assistance of mechanical ventilation in our follow-up study had a remarkably good long term prognosis. In a country such as South Africa, there is no question that, for VLBW infants, the provision of a neutral thermal environment, maintenance of fluid and electrolyte balance, blood glucose control, treatment of common infections and the provision of adequate nutrition, all of which form part of what can be defined as secondary level care, is affordable and appropriate given the excellent long term quality of survival.

However, as indicated above, the provision of intensive care which, *for the purposes of the discussion to follow is defined as the need for mechanical ventilation*, requires more careful consideration. In a country where there are vast disparities in the levels of health care available to different segments of the population, the question must be asked as to what role neonatal intensive care has to play.

7.3 The Role of Neonatal Intensive Care in South Africa

In considering the place of neonatal intensive in a developing country such as South Africa, two main issues need to be addressed.

1. Is it appropriate that neonatal intensive care should be provided?
2. If the answer to the first question is in the affirmative, how should infants be selected for admission, given that there will be inadequate numbers of beds available for all of those infants who may potentially benefit from such care?

7.3.1. Is Neonatal Intensive Care Justified in South Africa?

Approximately 20% of the population of South Africa is covered by medical insurance and health care for this section of the population is usually obtained in the private sector. Most private funders pay for neonatal intensive care although several have limits for hospital care and there is then pressure to move infants to public sector institutions when the limit is reached. Thus, neonatal intensive care is available for those able to afford private medical care. The political and ethical issues involved in the fact that one segment of a population has access to potentially life saving treatments on the basis of the fact that they are able to afford

it, be it directly or through medical insurance, are extremely complex and will only be addressed briefly here. Historically this was the case in most countries that are currently regarded as 'developed' and such inequalities exist in many countries of the world today including developed countries such as the United States (Beauchamp and Childress, 1994). Although this divide between those with access to private medical care and those without was previously along broad racial lines in South African, this is rapidly changing. Beauchamp and Childress (1994, pp351-355) discuss this subject in detail and reach the conclusion that such a two-tiered system can be justified within a framework for allocation of resources that coherently incorporates utilitarian and egalitarian principles. They argue further that where health care is socially funded, society's obligations are not limitless and that a 'decent' rather than an 'optimum' level of care should be the standard, but that the 'decent minimum' level of health care could be regarded as a right. Those with differing moral and ideological beliefs may challenge this conclusion from both sides: a person with a strongly libertarian view of society who would propose a free-market approach to health care would believe that this results in too high a level of taxation, while one with very strongly egalitarian beliefs would reject any form of a two-tiered system of health care.

In South Africa almost all sectors of society appear to have accepted that the level of health care will depend, at least in part, on the ability to pay for certain services. This discussion will therefore accept the basis of a two-tiered health care system and will focus on the provision of neonatal intensive care in the public health sector in the context of South Africa. This, however, does not imply that providers in the private health care sector do not have an obligation to undertake similar assessments of the available resources and to make ethical decisions within those constraints. As indicated previously, the provision of adequate

secondary level neonatal care appears to be within the means of the country and, as discussed, the enormous improvement in survival of VLBW infants at Baragwanath Hospital over the past 50 years has largely been due to good secondary level neonatal care rather intensive care and mechanical ventilation. Given these excellent results of secondary level care, it would be inappropriate to argue for the provision of neonatal intensive care if it were not possible to provide secondary level care for all who needed it - this, however, is not the case. The fact that there remain areas of the country where such care is inadequate either in terms of quantity or quality is a reflection of past political indifference to such needs and these gross inequalities are currently being addressed. Furthermore, while it is accepted for the purposes of this discussion that there will be inequalities in health care based on financial status, this author would argue that these inequalities should be minimised as far as possible. This is in keeping with the author's largely egalitarian philosophy, but there are other arguments in support of this. For example, South Africa has worse indicators of health status such as the infant mortality rate than other countries with a comparable Gross National Product and it is argued that this is largely due to the gross disparities in wealth amongst the population resulting in grossly unequal access to resources including health care (Bellamy, 1998). Thus a situation where there is unlimited access to neonatal intensive care for 20% of the population and none for the remaining 80% may be unacceptable philosophically as well as on the basis of the likely consequences. However, not all forms of tertiary care available in developed countries or in the private health sector in South Africa can be made available as part of the 'decent minimum' in the public sector on the basis of this argument. Which services amongst the many should be prioritised would depend on the cost and potential availability of such services as well as their effectiveness in terms of subsequent quality of life. Studies of the cost of neonatal intensive care in public sector hospitals in South Africa have shown that the cost is

modest in comparison with other areas of care - indeed it is not much more than the average costs of general patients in teaching hospitals (Ellis *et al,* 1991; Malan *et al,* 1992). Our studies and others have shown that, although there is a substantial mortality attached to neonatal intensive care, those that die usually do so relatively early during the course of their admission and the majority of infants are free of major handicap and are able to lead normal and productive lives.

Over the course of the last 30 years, neonatal intensive care units have developed in all of the larger centres in South Africa in public sector institutions. These units did not develop as part of a general health plan, but were developed by individuals or groups of individuals who were aware of developments in other parts of the world and initiated similar programs locally. As a result, based on calculations of the delivery numbers served by the major academic institutions, between one-quarter and one-third of infants born in the public health sector have some access to neonatal intensive care. It has also become accepted as an essential component of training of specialist paediatricians in this country in all of the academic institutions. Furthermore it is probable that, as evidenced by the excellent outcome in these studies of VLBW infants who did not require neonatal intensive care, the development of these units has had a major impact on the quality of care provided at secondary and even primary level in these institutions.

Thus neonatal intensive care has established itself *de facto* in the public health care sector in South Africa, at least in the urban areas. On the basis of the arguments developed above, this author would argue that this has been a development appropriate to the health needs of this country and that at least some 'quota' of neonatal intensive care is appropriate in the South

African context. The issues that now need to be addressed are how such services can be made more widely available in an equitable manner and, perhaps more important, how infants should be selected for neonatal intensive care, given the limitation of the resources both financial and human.

7.3.2. Who Should be Offered NICU Care?

At present, even in the institutions that do provide neonatal intensive care in the larger urban areas, there are insufficient beds to accommodate all of those who could benefit from such care. As indicated previously, the policy at Baragwanath Hospital with respect to admission of VLBW infants to the neonatal intensive care unit at the time of opening of the unit was that infants with birthweight <1000g would not be admitted for mechanical ventilation. This decision was an arbitrary one at the time, but has remained largely unchanged over the years and most public sector institutions have similar policies, albeit with minor variations to suit local circumstances and there has been much discussion over the years amongst neonatologists in South Africa regarding admission criteria to NICUs. These issues need to be addressed within a broad social and ethical context.

In her review on ethical decision making in neonatology with particular reference to neonatal intensive care, Kinlaw (1996) discussed three broad philosophical/ethical approaches to the care of critically ill neonates:

a. The "wait until certainty" approach which is largely that used in the United States where treatment is begun on almost every infant who is thought to have any chance of

survival and the most important guiding principle is to prevent the death of any infant who might survive with a fairly good outcome even at the expense of more survivors with severe handicaps.

b. The "statistical approach" determines categories of infants in which treatment may be limited or withheld. Here the most important guiding principle is to avoid creating severely handicapped infants at the expense of the deaths of some infants who may survive to lead normal lives. The example quoted is that of Sweden where infants born at a gestation of less than 25 weeks and weighing less than 600g may not be offered intensive care.

c. The "individualised approach" which is apparently practised in Britain is intermediate between the abovementioned approaches. It involves initiating care on any infant who has a chance of survival, but making a decision early, without necessarily waiting until certainty, on whether the individual infant is likely to have a favourable outcome and withdrawing intensive care treatment if it is felt unwarranted.

Kinlaw's entire discussion puts the interests of the individual infant at the centre of the ethical dilemma. Even in the case of the statistical approach, her interpretation of the guiding ethical principle is that the interests of the individual infant are best served by not initiating intensive care since the risks of survival with major handicap are too high. There is no mention in this review that there may be physical limitations of resources in the form of intensive care beds or indeed the resources of the society to care for handicapped children. This is representative of much of the literature on ethical decision making in neonatal intensive care which emanates

largely from developed countries and is thus not particularly helpful in developing policies in a country such as South Africa.

In their book on biomedical ethics, Beauchamp and Childress (1994) similarly stress the interests of the individual as the focal point of medical decisions in their discussions on the principles of respect for autonomy, nonmaleficence and beneficence, but in the section on justice (Beauchamp and Childress, 1994, pp326-394), they do address the issue of the limitations imposed by scarce resources.

Currently in the greater Johannesburg area, all of the public sector NICUs function in a cooperative manner to provide a regional service to the entire neonatal population. However, there are approximately 0.3 neonatal intensive care beds able to provide mechanical ventilation for each 1000 annual deliveries, whereas it is estimated that if all infants who may reasonably benefit from intensive care were admitted, the ratio should be approximately one intensive care bed per 1000 annual deliveries (unpublished data). Clearly therefore, selection for admission to the intensive care unit needs to take place. The principles of distributive justice, which refers to fair, equitable and appropriate distribution in society of resources, and the utilitarian maxim of triage, which would allow an NICU to do the greatest good for the greatest number (Beauchamp and Childress, 1994, p385), appears, in the author's opinion, to offer the most appropriate ways of selecting those infants who should be admitted to a neonatal intensive care unit. Since Baragwanath Hospital could not provide data on ventilating infants <1000g at birth, data from a previous study at Johannesburg Hospital at a time when infants <1000g were ventilated (Cooper *et al*, 1987) were re-analysed. The mean number of ventilator days to produce a survivor in each birthweight category was calculated by dividing the total number

of ventilator days for all infants in that birthweight category by the number of survivors. The results are shown in Table 7.1.

Table 7.1. Mean number of ventilator days to produce one survivor by birthweight category

Birthweight (g)	Number of Days
<1000g	41.1
1000-1499g	21.8
1500-1999g	12.1
>2000g	4.3

It can be seen that the resources required to produce one survivor from mechanical ventilation with a birthweight <1000g would produce almost two survivors with birthweight 1000-1499g, more than three survivors with birthweight 1500-1999g and almost ten survivors with birthweight >2000g. Thus, on the basis of the above principles, a birthweight/gestational age limit for admission to the intensive care unit should be one of the major criteria for admission to or exclusion from intensive care since this would allow a greater number of (larger) infants to benefit.

While gestation is usually a better indicator than birthweight of organ maturity and therefore prognosis, the majority of women delivering VLBW infants have not attended antenatal clinics. The estimation of gestational age under the stressful conditions of a critically ill newborn infant in the labour ward, initially by a relatively inexperienced medical practitioner may be substantially inaccurate. Thus for practical purposes, a birthweight limit rather than a gestational age limit is preferable. The question of where the limit should be set depends on

factors such as the availability of intensive care beds and the mortality and morbidity figures for that particular unit amongst other factors. This birthweight limit need only be absolute in one direction in the sense that all infants above that birthweight are eligible for intensive care, but that infants below that weight may occasionally be admitted if for example gestation has been carefully documented, perinatal care has been optimal and their clinical status immediately after birth gives cause for optimism.

In our situation, other groups of infants that are generally not admitted to the NICU, as mentioned in Chapter 5, are those with major congenital abnormalities that are either lethal or not compatible with a reasonable long term existence, those with severe hypoxic ischaemic encephalopathy following birth asphyxia which is known to be associated with a poor outcome, those with major intracranial haemorrhage or with any other condition where the prognosis is known to be poor. Given these exclusions, the birthweight limit of 1000g appears to be practically manageable in terms of the numbers of infants considered for admission. The fact that during 1990 at best only 26% of VLBW infants admitted for mechanical ventilation survived and were normal at 12-18 months of age, while about one-quarter of the survivors appeared to have definite physical handicaps is cause for reflection. To attempt to evaluate in detail whether these figures justify the current 1000g cutoff would require discussion around ethics and resource allocation that is beyond the scope of this thesis and would also require a similar detailed analysis on all other forms of expensive therapies - such information in the South African context is not available. However, in the opinion of this author, given the constraints of the overall health care system and the poor availability of resources to provide adequate support for children with handicap and their families, this is a rather depressing outcome and would not justify arguing for a lowering of the birthweight limit, but may even

suggest an increase in the limit. However, as mentioned previously, mortality of VLBW infants has improved substantially during the 1990s at Baragwanath Hospital and their outlook as the end of the decade approaches can be viewed more positively.

The discussion thus far has centred largely around what Beauchamp and Childress (1994) define as selection on the basis of medical utility. The criterion of social utility is more controversial. It has been suggested in discussions at local perinatal meetings that certain social factors such as a very young single mother, non-attendance at antenatal clinic or the perception that the infant is 'unwanted' should be considered when deciding on admission criteria to the intensive care unit. However, local data have shown that VLBW infants born to mothers who have not attended antenatal clinic do as well as those who have (Smith *et al,* 1995) while, in this follow-up study, antenatal attendance did not affect long term outcome either. Other social factors such as age of the mother, socioeconomic status and numerous other 'social utility' criteria had no effect on long term outcome except that developmental scores did correlate statistically with years of education that the mother had obtained. The latter, however, was not a strong correlation and could hardly be used to make decisions in this context. Thus, from our data there is no evidence to support the use of such criteria for admission to the intensive care unit and, since subjective judgements of social worth are usually involved, it would be difficult to justify such exclusions ethically. Given the political history of South Africa where adverse social criteria have often been determined by racial discrimination in the past, this approach is even more difficult to defend.

There are those who would argue against the use of principles such as utilitarianism in selecting who should be offered forms of treatment that are not available to all who need it.

On the basis that all individuals have equal worth, they would argue that discriminating against some on the basis of factors such as birthweight is unjust (Beauchamp and Childress, 1994). It would seem that this argument cannot be reconciled with the philosophy outlined above using 'medical utility' criteria as the basis of selection and represents a fundamental difference in philosophical approach from that used by this author. However, having set rational and coherent medical criteria for admission, it nevertheless happens frequently that there are still not sufficient NICU beds for the numbers of infants requiring them. Here the argument for impersonal mechanisms of chance and queuing as outlined by Beauchamp and Childress (1994, pp382-384) appears to offer a solution. These authors give the example of a centre in the United States where candidates for renal transplant were selected on a lottery system. In the intensive care situation, the concept of queuing for intensive care beds would be more logical than a lottery, recognising that a number of such infants will die before an intensive care bed becomes available. This author would agree with Beauchamp and Childress (1994) however, that the use of such a system can be applied only to those categories of patients with no major disparities in medical utility.

As the criteria for admission to the neonatal intensive care in a situation such as ours need to be stricter than in situations where more facilities exist, so the criteria for withdrawal of care needs also to be stricter based on the same philosophy of maximising the resources for the good of the greatest number. Although Beauchamp and Childress (1994, p199) argue convincingly that there is no moral distinction between not initiating and withdrawal of care, there is no doubt that it is far more difficult emotionally for both caregivers and parents to withdraw intensive care once initiated. Thus having used the statistical approach as outlined earlier in this chapter on the basis of triage for admission to the NICU, the individualised

approach rests more comfortably and acceptably with all concerned when decisions regarding withdrawal of care are involved. However, once again it is important to base these decisions on medical utility which in this case is based largely on prognosis for an acceptable outcome. Criteria for withdrawal of care would include the development of complications such as PVL and severe chronic lung disease. It is important that such decisions are taken in a consistent manner since there is a great danger that ad hoc and inconsistent decisions regarding withdrawal of care may be made simply because there is an infant with a better prognosis requiring a bed. It is also important to consider the opinion of Kinlaw (1996) that decision makers should be wary of the "tyranny of the normal" in which the only acceptable outcome is a normal, healthy, cognitively intact individual. However, in the context of a country with poor resources to support those with handicap, this opinion needs to be considered with caution.

Finally, the role of the parents in the paradigm of decision-making in the NICU in the context of limited resources needs to be considered. Once again issues differ from those that usually form the basis of discussion in the literature emanating from developed countries. Paris and Schreiber (1996) discussed the role of parental discretion in the refusal of treatment of the newborn infant and considered it as a real but limited right. Similarly Engelhardt (1975) argued that "society has a right to intervene and protect children for whom parents refuse care when such care does not constitute a severe burden and when it is likely that the child could be brought to a good quality of life". In the situation faced in South Africa the opposite paradigm frequently occurs where care cannot be offered to infants whose parents may desire it. It is highly likely that, if parents were given the choice of whether or not their infants who weighed <1000g at birth should be offered intensive care therapy, they would choose in the

affirmative. To illustrate this, a study was conducted at Baragwanath Hospital by Wainer and Khuswayo (1993) in which mothers whose infants had 'graduated' to the low care wards were asked the theoretical question as to whether they would consider intensive care should be continued if it was highly likely that their child would survive with major brain damage. Close to 100% of the mothers answered that such care should be continued. Accepting the limitations of such a study where theoretical questions are asked, but the full implications of such a decision may not have been appreciated, this nevertheless illustrates the serious difficulties that institutions and individuals working in these institutions face. While policies may be based on sound philosophical and ethical principles where the greatest good is done for the greatest number of people, such policies may frequently be in conflict with the individual wishes of patients and, in this case, the wishes of their parents. It may be accepted that in situations such as these where resources are limited and must be rationed, the wishes of society may override the wishes of the individual. This, however, presupposes that these are actually the wishes of society. In South Africa until now there has been little tradition of discussions in civic society around matters such as these. It is therefore essential to initiate these discussions so that ultimately such policies can legitimately be held up as the wishes of society.

APPENDIX A

SUMMARY FORM FOR ALL INFANTS ADMITTED TO NICU

(Fill in relevant details and circle **all** applicable options -
form to be completed on death or discharge from NICU)

Surname **Date of Birth (dd/mm/yy)**

First Name: Mother **Baby**

Hospital No: Mother **Baby**

Birthweight (g) **Gestation (wks)**

Booked (y/n) **Sex (m/f)**

Date of Admission to NICU **Skull circ** **cm**

Admitted to NICU from (state ward/hosp)

Place of Birth

01 = Bara
02 = Soweto Clinic
03 = Other hosp/clinic
04 = Home/other

Outside referrals - Dr & hospital/clinic .....

.....

Maternal Details: Age (yrs) **Grav** **Para**

Place of Residence:

01 = Soweto
02 = Johannesburg suburbs
03 = Alexandra
04 = Elsewhere

Pregnancy Details:

01 = WR negative
02 = WR positive
03 = WR unknown
04 = Prom >24 hrs
05 = Mec stained liquor
06 = Offensive liquor
07 = Twins
08 = Triplets or more
09 = Diabetes
10 = PET
11 = Antepartum haemorrhage
99 = Other (specify)

Mode of Delivery:

01 = Vertex
02 = Breech
03 = Face
04 = Brow
05 = Compound
99 = Unknown
06 = Forceps
07 = Vacuum
08 = Failed Forceps
09 = Failed Vacuum
10 = Caesar

Apgars: 1 min ..... 5 min .....

IPPR at birth via: 01 = Mask 02 = ET tube

Time to spontaneous resp (if applc) (min)

1. RESPIRATORY

01 = Hyaline membrane dis
02 = Transient tachypnea
03 = Meconium aspiration
04 = Pneumonia, congenital
05 = Pneumonia, acquired
06 = Pulmonary haemorrhage
07 = Congenital abnormality
08 = Severe apnea
09 = Pneumothorax
10 = Chest drain(s)
11 = Other air leak / Interstit air
12 = Post extubat atalectasis
13 = Post extubat stridor
14 = Chronic lung disease eg BPD
15 = Theophyllin Rx
99 = Other (specify)

Primary Indication for Ventilation

01 = Respiratory
02 = CNS (eg asphyxia)
99 = Other (specify)
03 = Cardiac
04 = Post surgery

ICU Bed Number (1 - 12): (If moved, state last bed no.)

Date of first intubation (dd/mm/yy)

Date of final extubation/death (dd/mm/yy)

Highest Peak Pressure **Highest Rate**

No. of days in >60% Oxygen **In 40 - 60% Oxygen**

Drugs:

01 = Pavulon
02 = Decadron

Failed extubation (state number)

2. CENTRAL NERVOUS SYSTEM

01 = Intraventricular Haem
02 = Intracerebral Haem
03 = Subaponeurotic
04 = Subdural/subarachnoid
05 = Convulsions
06 = Post haemorr hydroceph
99 = Other (specify)
07 = Asphyxia
08 = Cerebral oedema
09 = Postasphyxial encephalopathy
10 = Meningitis
11 = V-P Shunt
12 = Cong malform (+ hydroceph)

Intraventricular Haemorrhage (01 above) Grade (1 - 4) :

Postasphyxial Encephalopathy (09 above) state details:

3. CARDIOVASCULAR SYSTEM

01 = Patent ductus
02 = Persistent fetal circ
03 = Arrythmia
04 = Hypertension
05 = Tricusp incomp (hypoxic)
99 = Other (specify)
06 = Indocid
07 = Pressors (eg dopamine)
08 = PDA ligated
09 = Antihypertensives
10 = Congenital heart disease

4. **GASTROINTESTINAL/NUTRITION**

01 = Meconium plug
02 = Bile stained aspirates
03 = Bloody stools
04 = Suspected NEC
05 = Definite NEC
06 = Obstructive jaundice
99 = Other (specify)
07 = Feeds withheld < 5 days
08 = Feeds withheld > 5 days
09 = Hyperal (amino acids)
10 = Intralipid
11 = Surgery
12 = Congenital malformation

5. **RENAL**

01 = Renal failure/dysfunc
02 = Acute tubular necrosis
03 = Cortical necrosis
99 = Other (specify)
04 = Dehydration/prerenal
05 = Syphilic renal disease
06 = Congenital malformation

6. **HAEMATOLOGY/JAUNDICE**

01 = Anemia day 1 (<12g%)
02 = Polycythemia (Hct >65%)
03 = Leucopenia (<5000)
04 = Leucocytosis (>25000)
05 = Thrombo/penia (<100000)
06 = Petichiae
07 = Rh Hemolysis
08 = Other Hemolysis
09 = Phototherapy
10 = 1 Exchange
11 = Multiple Exchanges
12 = DIC
13 = Haemorrhagic disease of newborn
99 = Other (specify)

Peak Bilirubin:

7. **METABOLIC**

01 = IDM
02 = Hypoglycemia) if
03 = Hyperglycemia) required
04 = Hypocalcemia) treatment
05 = Hypernatremia (>150)
06 = Hyponatraemia (<125)
07 = Hyperkalemia (> 6.5)
08 = Hypokalemia (< 3.0)
09 = Metabolic acidosis
99 = Other

8. **INFECTIONS**

01 = Cong syphilis-symptomatic
02 = Suspected sepsis
03 = Septicemia (proven)
04 = Meningitis
05 = Renal tract infect
06 = Bone and/or joint infec
07 = Syphilitic bone disease
99 = Other (specify)
08 = Rubella
09 = Toxoplasmosis
10 = CMV
11 = Herpes
12 = Fungal
13 = Hepatosplenomegaly (>3cm)
14 = Splenomegaly (palpable)

Organisms Cultured (not surface cultures)	**Age <48 hrs at time of culture (y/n)**	**Site** (eg. CSF, art line, venous)

9. DRUGS

Antimicrobials (list all those used)

Other drugs (list all those used)

10. CONGENITAL ABNORMALITIES

01 = Extra digits
02 = Cong abnormality (not 01)
99 = Known teratogens (specify)
03 = Consanguinity
04 = Siblings affected

For Congenital Abnormalities (excluding extra digits)

Residential address during first trimester

Details of anomalies

11. OUTCOME

Date of Discharge from NICU (dd/mm/yy)

Death (y/n) **Place of Death (ward)**

Date of Death (dd/mm/yy)

Cause of Death (choose the most important - give further details below)

01 = Asphyxia
02 = Prematurity
99 = Other (specify)
03 = Infection
04 = Congenital Abnorm

12. ADDITIONAL REMARKS

(Including as much detail as possible as to Cause of Death eg. if prematurity, state HMD, IVH etc; or if additional cause of death eg. if prematurity chosen above - add in asphyxia or infection here if relevant).

APPENDIX B

BARAGWANATH HOSPITAL - NEONATAL RECORD CHART

Surname **Date of Birth** **Time**

First Name: Mother **Baby**

Hospital No: Mother **Baby**

Birthweight (g) **Gestation (wks)**

Booked (y/n) **Sex (m/f)**

Head Circ on Adm (mm) **Date of Adm to Neonatal Ward**

Place of birth

01 = Bara 02 = Soweto Clinic 03 = Other Hospital 04 = Home/Other

Outside Referrals - Dr & Hospital .....

Maternal Details: **Age (yrs)** **Grav** **Para**
No. Alive **No. Dead** **Stillbirths** **Miscarriages**

Address

Pregnancy Details: Maternal Blood Group .....

01 = WR negative	04 = PROM >24hrs	07 = Twins	10 = PET
02 = WR positive	05 = Meconium liquor	08 = Triplets/more	99 = Other (Specify)
03 = WR unknown	06 = Offensive liquor	09 = Diabetes	

Mode of Delivery

01 = Vertex	04 = Brow	07 = Vacuum	10 = Caesar
02 = Breech	05 = Compound	08 = Failed Forceps	11 = Unknown
03 = Face	06 = Forceps	09 = Failed Vacuum	

Apgars: 1 min 5 min

IPPR at birth via: 01 = Mask 02 = ET tube

Time to spontaneous resp (if applic) (min)

OUTCOME

All wards admitted to:

Death (y/n) **Date of Death** **Place of Death (ward)**

Discharge Details: **Weight** **Date** **Ward**

CAUSE OF DEATH (choose the most important - give further details below)

01 = Asphyxia	03 = Infection	
02 = Prematurity	04 = Congenital Abnorm	99 = Other (specify)

COMMENTS:

Appointment for Neonatal Follow Up (y/n)

1. **RESPIRATORY**

01 = Hyaline Membrane dis 03 = Meconium aspiration 05 = Pneumonia, acquired
02 = Transient Tachypnea 04 = Pneumonia, congenital 14 = Chronic lung dis.

Number of days: Ventilated ..... Headbox Oxygen ..... Incubator Oxygen .....

Other respiratory problems:

2. **CENTRAL NERVOUS SYSTEM**

01 = Intraventr haem Grade 05 = Convulsions 07 = Asphyxia
03 = Subaponeurotic Haem 06 = Post Haem Hydroceph 09= Postasphyx Encephal
Other problems (including details of post asphyxial encephalopathy):

3. **CARDIOVASCULAR SYSTEM**

01 = Patent ductus 06 = I[illegible]ocid 10 = Cong ht disease
Other problems:

4. **GASTROINTESTINAL SYSTEM**

04 = Suspected NEC 05 = Definite NEC
Other problems:

5. **RENAL Problems:**

6. **HAEMATOLOGY**

Peak Bilirubin:
09 = Phototherapy 10 = 1 Exchange 11 = Multiple exchanges
Other problems:

7. **METABOLIC Problems:**

8. **INFECTIONS**

01 = Congenital syphilis 03 = Septicaemia (proven) 04 = Meningitis
Organisms cultured (site and dates)

Other Problems:

9. **DRUGS** (List all drugs given)

10. CONGENITAL ABNORMALITIES

01 = Extra digits
02 = Cong abnormality (not 01)
99 = Known teratogens (specify)
03 = Consanguinity
04 = Siblings affected

For Congenital Abnormalities (excluding extra digits)
Residential address during first trimester & details of anomalies

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