

BORN TOO SOON



Conception



First Month



Second Month



Third Month



Fourth Month

Formation of the human foetus

BORN TOO SOON

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INTRODUCTION

Preterm birth is a major world health problem. Statistics show the significant numbers of perinatal deaths due to preterm birth and the disproportionate numbers of children surviving preterm birth who suffer from physical and intellectual impairment. The problem affects countries in both the developed and the under developed world. Although the impact on third World countries differs as the prevalent disease states, malnutrition and limited medical facilities reduce the chances of survival.

In the Western world, during the last 20 years there have been tremendous advances in neonatal intensive care leading to a remarkable improvement in the prospects of the very small preterm infant. In a twelve year survey (1980-91), at Hammersmith hospital, London, of neonatal unit admissions of inborn infants (that is booked or referred to the hospital 'in-utero') it can be seen that there has been considerable improvement in the survival of extremely preterm low birthweight infants (Tables 1 and 2). In 1991 for infants of between 28 weeks gestation (12 weeks early) and 31.9 weeks there was a 95 per cent survival rate and for infants of less than 26 weeks gestation a 40 per cent survival rate. The advances in neonatal care are particularly marked when looking at the survival of infants weighing less than 749g. In 1980-83 there were no survivors, by 1988-91, whilst numbers are small, there was a 15-67 per cent survival rate for these infants.

The very success of intensive care has led to new ethical dilemmas for both healthcare professionals and parents. Should attempts be made to resuscitate all preterm infants regardless of maturity? Is it ethical to withdraw intensive care treatment from a baby with severe brain damage? Is neonatal intensive care for the extremely preterm infant an appropriate use of scarce and expensive medical resources? It is too easy to allow the ability to preserve the lives of increasingly preterm infants to blind society to the ethical dilemmas concerning the costs and value of treating these infants and it is hoped that this paper will help open the discussion of what is for some, a highly emotive subject.

Several studies have attempted to assess the cost of neonatal intensive care, however because of the difficulties of accurate cost assessment, particularly in the NHS, the figures should be treated with caution. Sandhu et al (1986), using 1984 prices, estimated that the cost per patient/day was £300 for neonatal intensive care, £140 for intermediate care and about £70 for nursery care. At today's prices these would be approximately doubled. Salary costs (especially those of nursing staff) account for more than 50 per cent of the total budget.

**Table 1 Neonatal admissions inborn 1980-1991 (N=2501)
Percent survival by gestation***

Year	Weeks					
	22-25.9	26-27.9	28-28.9	29-29.9	30-30.9	31-31.9
1980	0% (0/1)	25 (2/8)	100 (5/5)	92 (12/13)	83 (10/12)	100 (8/8)
1981	33 (1/3)	40 (4/10)	64 (18/28)	82 (14/17)	94 (15/16)	96 (26/27)
1982	-	50 (10/20)	75 (3/4)	88 (7/8)	89 (16/18)	96 (25/26)
1983	100 (1/1)	81 (13/16)	100 (16/16)	100 (18/18)	100 (8/8)	100 (22/22)
1984	40 (2/5)	62 (13/21)	89 (16/18)	100 (12/12)	83 (10/12)	100 (30/30)
1985	80 (4/5)	80 (16/20)	62 (8/13)	100 (8/8)	88 (14/16)	94 (17/18)
1986	0 (0/3)	73 (24/33)	71 (5/7)	79 (11/14)	92 (11/12)	100 (23/23)
1987	38 (3/8)	41 (9/22)	80 (12/15)	92 (11/12)	95 (19/20)	100 (20/20)
1988	29 (2/7)	54 (12/22)	71 (12/17)	69 (9/13)	100 (8/8)	97 (29/30)
1989	57 (4/7)	50 (6/12)	78 (14/18)	89 (16/18)	67 (10/15)	100 (13/13)
1990	15 (2/13)	45 (10/22)	67 (6/9)	60 (6/10)	94 (17/18)	100 (12/12)
1991	40 (2/5)	56 (5/9)	100 (7/7)	75 (6/8)	100 (17/17)	100 (6/6)

*Excludes infants born with lethal congenital abnormalities.

Source: Ahmed & Watson, 1992.

Since preterm infants usually remain in hospital for many weeks, largely dependent upon their gestational age at birth, costs per preterm infant are high. It has been estimated that the approximate cost of admission of a preterm infant at a London teaching hospital would range from £6,000 per infant at 28 weeks to £20,000 at 24 weeks (Wyatt & Spencer, 1992).

In the UK, there is currently a nationwide shortage of neonatal intensive care cots. This problem is particularly acute in London and the South, and is made worse by a shortage of appropriately qualified neonatal intensive care nurses. In 1989, the neonatal intensive care unit of a London teaching hospital refused over 300 requests for admission from other hospitals because of a shortage of intensive care cots. Many of these infants eventually found places in other units, but some did not. The outcome for infants not admitted to a regional neonatal intensive care unit is recognised to be substantially impaired. In the light of a scarcity of resources and pressure on existing facilities some very difficult clinical decisions about intensive care for the preterm infant have to be made.

The epidemiology and the causes of preterm birth are considered in this paper (see pages 6-19). As will be seen there is still much to learn about the causes of early delivery and it is important that more research is conducted in this area to improve our understanding in order that effective prevention programmes might be adopted.

However, even with our limited knowledge, countries which have introduced prevention programmes have reduced their rates of preterm birth by as much as 30 per cent. Given the extent of physical and mental impairment among survivors of extremely preterm birth, it has been estimated that 20 per cent of survivors will have significant neurodevelopmental impairment (see page 29), prevention clearly has an important role to play. Potential preventive efforts include true primary prevention, early identification of preterm labour or its premonitory signs and inhibition of labour. The prevention of preterm birth is discussed in more detail later in the paper (see pages 31-38).

**Table 2 Neonatal admissions inborn 1980-1991 (N=2501)
Percent survival by birthweight***

Year	Birthweight			
	<749g	750-999g	1000-1249g	1250-1499g
1980	0% (0/1)	50 (5/10)	90 (18/20)	100 (18/18)
1981	0 (0/3)	46 (11/24)	85 (29/34)	96 (25/26)
1982	0 (0/3)	72 (13/18)	85 (22/26)	96 (23/24)
1983	0 (0/1)	89 (16/18)	96 (27/28)	100 (23/23)
1984	33 (2/6)	63 (17/27)	89 (33/37)	100 (29/29)
1985	33 (2/6)	85 (23/27)	77 (17/22)	100 (32/32)
1986	36 (4/11)	74 (14/19)	87 (27/31)	90 (19/21)
1987	30 (3/10)	56 (14/25)	86 (25/29)	96 (22/23)
1988	29 (2/7)	52 (11/21)	73 (22/30)	94 (33/35)
1989	33 (2/6)	53 (10/19)	78 (14/18)	90 (26/29)
1990	15 (2/13)	36 (8/22)	86 (19/22)	96 (27/28)
1991	67 (6/9)	64 (9/14)	88 (7/8)	100 (17/17)

*Excludes infants born with lethal congenital abnormalities.

Source: Ahmed & Watson, 1992.

EPIDEMIOLOGY AND THE CAUSES OF PRETERM BIRTH

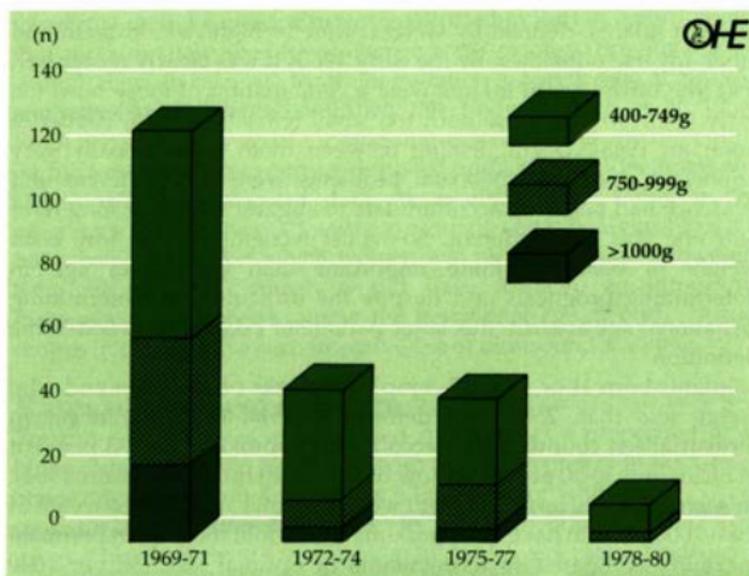
In the Western World, preterm birth is the major cause of infant mortality (McCormick, 1985). One in 20 births but two out of three perinatal deaths are associated with preterm birth (Lumley, 1987a). Surviving preterm infants have a greatly increased risk of acute and chronic illnesses and a variety of neurodevelopmental handicaps. These facts make the the epidemiology of preterm birth a matter of importance. In addition, the epidemiology of preterm births is worthy of attention since it may help both with the identification of high risk groups of women who may be subjects for intervention or treatment, and perhaps more importantly it may assist in the clarification of the aetiology of the phenomena

Definitions

A fundamental problem in the counting of births is the stage of gestation at which conceptions are first registered. Japan registers stillbirths, also known as late fetal deaths, from 12 weeks gestation, Norway from 16 weeks, Australia from 20 weeks, California from 22 weeks and most European countries from 28 weeks gestation (Mugford, 1983). The differences which these definitions introduce into the data systems only have a small effect on the total numbers of births but they have a major effect on the total numbers and crude rates of perinatal deaths.

In theory there should be fewer, if any, problems with the registration of live births since the internationally agreed definition is 'the complete expulsion or extraction from its mother of a product of conception, irrespective of the duration of the pregnancy, which after such separation, breathes or shows any other evidence of life, such as a beating of the heart, pulsation of the umbilical cord, or definite movement of the voluntary muscles, whether or not the umbilical cord has been cut or the placenta is attached' (World Health Organisation, 1977). However, in practice, whether a fetus is born liveborn or stillborn at midpregnancy, around the registration boundary, depends in part on how aggressive the management of labour and delivery is. In addition, one or more of the signs of life mentioned may be present in a fetus born early in the second trimester of pregnancy. A number of factors prompt the differentiation of a spontaneous abortion and a livebirth: in particular, the weight or gestational age criteria for registration of stillbirths, the gestation at which maternity benefits are payable, whether registration makes the parents liable to pay for a burial, and the perceived viability of the

Figure 1 Infants weighing at least 400g, excluded from registration as 'previabie' in one teaching hospital 1969-80.



Source: Lumley, 1987a.

fetus or infant. Better chances of survival among very tiny infants encourage assisted delivery, elective resuscitation and registration and can produce an apparent increase in very preterm births (Mutch et al, 1981).

Figure 1 shows the numbers and birth weights of 'previabie'¹ fetuses, recorded at one teaching hospital from 1969 to 1980. During this period, in 1974 the definition of stillbirth changed and a neonatal intensive care unit was established at the hospital in 1976. These data also confirm the earlier point that the effect of exclusions at the boundaries of registration is trivial in terms of births only (only 0.9 per cent of births were excluded in 1969-71 and only 0.2 per cent in 1978-80) but that the effect on perinatal deaths is marked: 27 per cent of deaths were excluded in 1969-71, 6.3 per cent in 1978-80. Prematurity raises other definitional issues. It was defined for many

1 Previabie fetus - one which is considered to be born too early or too small to survive. Due to medical advances in recent years the number of babies born in this category has been reduced.

years as the birth of an infant weighing 2500g or less. The appropriateness of the definition lay in the fact that birth weight was the most frequently and reliably recorded measure for infants and that preterm infants, defined by weight, were at high risk of death and other adverse outcomes. By the early 1960s it was clearly recognised that low birth weight infants were a combination of those born too early (*preterm*) and those born too small (*growth retarded*) (Butler & Bonham, 1963). Distinguishing between them was clinically very important since their neonatal problems were very different and evidence had begun to accumulate to suggest that their long term outcome was also different. So whilst recognising that low birth weight is relatively more important than gestational age in determining prognosis and despite the difficulties in determining gestational age at birth, this latter parameter became included in the definition.

Infants born at or after 37 completed weeks of gestation and who weigh less than 2500g are defined as *term, low birth weight*. In industrialised countries they account for approximately 2-3 per cent of births and 30-50 per cent of low birth weight infants (Ericson, 1984). In such countries term low birth weight infants are likely to weigh at least 2000g and to have an approximately 10 fold increase in perinatal mortality compared to term infants of optimal size (30 per 1000 compared to 30 per 1000). The contribution of mature infants to the incidence of low birth weight in developing countries is much greater (Villar & Belizan, 1982).

Preterm birth is a birth before 37 weeks gestation or less than 259 days since the first day of the last menstrual period (World Health Organisation, 1977). The classification of preterm, low birth weight and preterm is not entirely satisfactory for a number of reasons. The first is that it includes two cut off points, for weight and gestation, which do not denote dramatic shifts in fetal survival or physiological maturity. The second reason is that up to half of all preterm infants in some societies weigh 2500g or more and are not of low birth weight (Ericson et al, 1984). These are well grown, slightly immature infants who may present early problems of management but have not been shown to have any excess mortality or major morbidity.

The definition of preterm, given above, even after the exclusion of infants with a birth weight at or over 2500g links together very diverse groups of infants, for example, those born at 22 weeks and weighing 500g and those born at 34 weeks weighing 2000g as well as those who are both preterm and growth retarded, 34 weeks and 1200g. Ideally these infants need to be divided into categories which take account of their immaturity and the associated presence/absence of growth

retardation. Unfortunately this requires accurate information about gestational age.

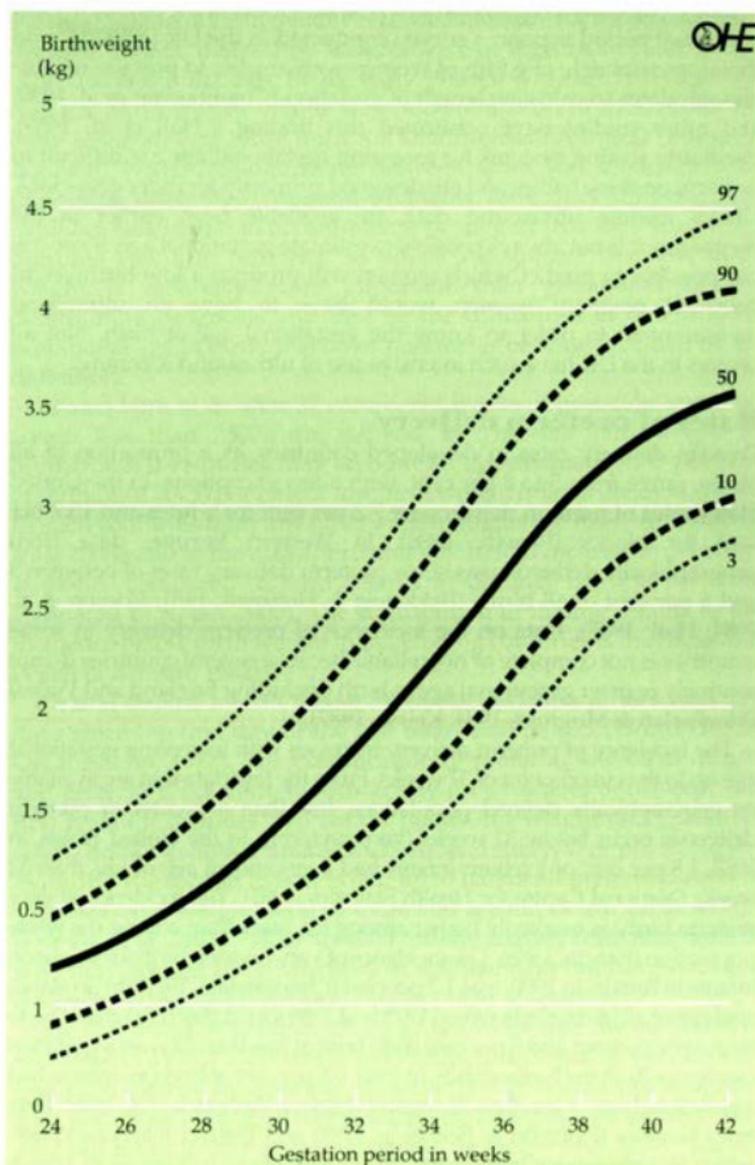
It has long been recognized that a woman's recall of the date of her last menstrual period is poor; a survey conducted in the UK in 1970 found that approximately one fifth of women were unable to provide reliable enough dates to calculate length of gestation (Chamberlain et al, 1970) and other studies have confirmed this finding (Hall et al, 1985). Paediatric scoring systems for assessing gestational age are difficult to perform on these babies and are designed primarily for older gestations. Unless reliable ultrasound data are available from earlier in the pregnancy it is not always possible to estimate gestational age. Since it is not possible to predict which women will produce a low birthweight baby all pregnant women would have to have an ultrasound measurement in order to know the gestational age at birth. Not all centres in the UK have such intensive use of ultrasound scanning.

Rates of preterm delivery

Preterm delivery rates in developed countries, as a proportion of all births, range from 5 to 8 per cent, with a few exceptions. In the United States rates of preterm delivery are 7.2 per cent for whites and 15.7 per cent for blacks (Paneth, 1986). In Western Europe, data from geographically defined areas show preterm delivery rates of between 5 and 8 per cent of all births (Bakketeig & Hoffman, 1981; Ericson et al, 1984; Hall, 1985). Data on the incidence of preterm delivery in some countries is not complete or not reliable because several countries do not routinely register gestational age at birth (including England and Wales) (MacFarlan & Mugford, 1984; Keirse, 1987).

The incidence of preterm delivery increases with increasing gestational age up to the cut off point of 37 weeks. From the few data that are available on geographically defined populations, less than a quarter of preterm deliveries occur below 32 weeks (very preterm). In the United States, in 1983, 1.8 per cent of liveborn infants had a gestational age of less than 32 weeks (National Centre for Health Statistics, 1985). The incidence of very preterm births is markedly higher among the black than among the white population (Paneth, 1986). The incidence of very preterm birth for singleton infants in Britain, in 1970, was 1.2 per cent (Chamberlain, 1975). In Scotland, analysis of all livebirths between 1975 and 1989 found that 0.7 per cent were born very preterm and 5 per cent were born at less than 37 weeks gestation (see figure 2). In the Netherlands, in 1983, 0.6 per cent of liveborn infants had a gestational age of less than 32 weeks (Verloove-Vanhorick et al, 1986). Data from Norway (Hoffman & Bakketeig, 1984) and Finland (Heinonen, 1988), which include infants born in the 32nd week, show incidences of 1.5 per cent of all singleton births and 1.1 per cent of live births respectively.

Figure 2 Centile growth curves for Scotland 1975-1989
All Singletons



Recent changes in preterm delivery rates

Preterm births in France fell from 8.2 per cent to 5.6 per cent of all births between 1972 and 1981 with an improvement in the rates below 34 weeks as well as in the mildly preterm group (Papiernik et al, 1985a). The reasons for the decline in preterm birth in France will be discussed in the section on the prevention of preterm births. In contrast with France, most countries preterm delivery rates have remained relatively stable in the past twenty years. Over a longer time period it is possible to show that there have at least been some regional declines in some countries: in Aberdeen, for example, the preterm delivery rate fell from 9.3 per cent in 1951-55 to 6.8 per cent in 1976-80 (Hall, 1985).

Categories of preterm birth

A retrospective study of preterm births (excluding those with lethal malformations) in Oxford between 1973 and 1975 (Rush et al, 1976) found that a significant proportion of them were the result of elective delivery, indicated on maternal or fetal grounds, for example severe pre-eclampsia², maternal renal disease or fetal growth retardation. This group accounted for 28 per cent of all preterm births. A second group included those where preterm labour was complicated by additional adverse factors such as antepartum haemorrhage³ or ruptured membranes and were 22 per cent of the total. The largest group of preterm births, 40 per cent, were characterised by spontaneous (idiopathic) preterm labour without additional complications. In Oxford, those infants delivered electively had a significantly better perinatal outcome than the other two groups even taking into account birth weight and gestational age.

In a retrospective study carried out in Dundee (Walker & Patel, 1989), where there has been a policy of routine ultrasound screening at 19 weeks gestation, all pregnancies ending between 20 and 28 weeks over a five year period (1980-84 inclusive) were reviewed to determine what antenatal factors resulted in these late abortions and very preterm deliveries. During the five year period 144 mothers gave birth to 156 infants (12 sets of twins). Seven of the women had not had an ultrasound scan before 20 weeks gestation and were excluded from the study. Of the 149 remaining infants, 99 were registered as

2 Pre-eclampsia – first stage of pregnancy toxæmia characterised by raised blood pressure, limb swelling, and presence of albumin in the urine.

Eclampsia – a complication of pregnancy comprising high blood pressure, the passage of proteins in the urine, headaches, visual disturbances, and occasionally convulsions.

3 Antepartum haemorrhage – bleeding from the vagina before delivery.

abortions. Of the 50 infants who were liveborn, 21 died within one week, another three died within one month and a further two within 18 months. Mean birthweight between 25 and 26 weeks gestation was 681g, between 26 and 27 weeks 889g and between 27 and 28 weeks was 978g. Of the 24 surviving infants eight were found on follow up to have a major degree of handicap (although in one case the disability was congenital in origin). The Dundee study (see Table 3) found that the most frequent precipitating cause of delivery was uncomplicated spontaneous preterm labour (47 per cent).

Table 3 The causes of delivery between 20 and 28 weeks gestation and the subsequent infant outcome in 149 infants (1980-84)

<i>Cause</i>	<i>Stillborn or abortion</i>	<i>Live <7 days</i>	<i>Died 8-28 days</i>	<i>Died 1-18 months</i>	<i>Alive (handi-capped)</i>	<i>Alive (well)</i>	<i>Total</i>	<i>Per-centage</i>
Premature labour	39	14	3	2	5 ^(a)	8	71	47.7
Antepartum haemorrhage	15	5			3 ^(b)	3	23	15.4
Preterm spontaneous rupture of membranes	15	1				2	21	14.1
Unexplained IUD	7						7	4.7
Intrauterine growth retardation	2						2	1.3
Intrauterine asphyxia	1						1	0.7
Fetal abnormality	3						3	2.0
Hypertension	4					3	7	4.7
Cervical incompetence	5	1					6	4.0
Maternal disease	1						1	0.7
Infection	7						7	4.7
Total number (per cent)	99 (66.4)	21 (14.1)	3 (2.0)	2 (1.3)	8 (5.4)	16 (10.7)		

Type of disability:

(a) Right hemiplegia: right hemiplegia: blind: blind: osteogenesis imperfecta.

(b) Left hemiplegia: microcephaly: spastic dysplegia.

Source: Walker & Patel, 1989.

Epidemiological associations

Classic epidemiological associations of preterm birth have been found repeatedly in Europe and North America over the past 25 years. The associations, which tend to be interrelated, are those of poverty and relative social disadvantage (see Table 4). However, the relative risks are small except for teenage multiparity.

The 'weighting' of preterm births by those infants born after 34 weeks gestation means that the classic epidemiological associations are those of mild rather than extreme immaturity. It should not be assumed that the associations apply with equal strength to all categories of preterm birth. In the past 30 years, three American studies have found that the risk factors for very low birthweight babies are not identical to those for low birthweight and that socioeconomic status and maternal height, for example, are not associated with very low birthweight (Wilson et al, 1963; Levkoff et al, 1982; Nelson & Ellenberg, 1985). Table 5, which uses birthweight groupings as a surrogate for gestation categories, shows how the association with socioeconomic status, so powerful in the whole data set, vanishes for infants below 1000g when they are considered by themselves (Lumley et al, 1985a).

Population-based birthweight data from Scotland confirm that social class differences are marked for low birthweight (5.3-9.8 per cent), marginal for infants between 1000-1500g (1.0-1.8 per cent) and virtually non-existent for infants below 1000g (0.6-0.9 per cent) (MacFarlane & Chalmers, 1981). A similar finding has been made in Sweden (Ericson et al, 1984). In contrast, black infants in the USA are

Table 4 Social and demographic associations of preterm delivery

		<i>Relative risk</i>
Primipara <20 years	(N)	1.5
>34 years	(N)	1.1
Primipara unmarried	(N)	1.7
Multipara <20 years	(N)	5.2
Education <11 years	(N)	1.4
Combined social index	1 - high (S)	1.0
	2 - intermediate (S)	1.3
	3 - low (S)	1.8
Black (US)		2.3
Aboriginal (AUS)		1.9

(N) Norway, (S) Sweden, (US) United States of America, (AUS) Australia.

Sources: Bakkeiteig & Hoffman 1981, Committee to Study the Prevention of Low Birth Weight 1985, Ericson et al 1984.

Table 5 Socioeconomic status and low birthweight, Tasmania 1982-84

Socioeconomic status	Singleton births (per cent)			No.	Relative risk	
	<1000g	1000-1499g	1500-2499g		ELBW+	All LBW
I and II	0.3	0.4	2.6	3,733	1.00	1.00
III	0.4	0.4	3.9	7,283	1.31	1.46*
IV	0.3	0.4	4.1	2,425	1.12	1.51*
V	0.3	0.4	4.2	3,480	1.17	1.53*
VI	0.6	0.9	5.5	3,925	1.91	2.21*
Total	0.4	0.5	4.0	20,846		

*95 per cent confidence limits of the relative risk do not include 1.0
LBW births <2500g

I professional, II intermediate, III skilled, IV semiskilled, V unskilled, VI unemployed (includes single women).

+ ELBW = Extremely low birthweight

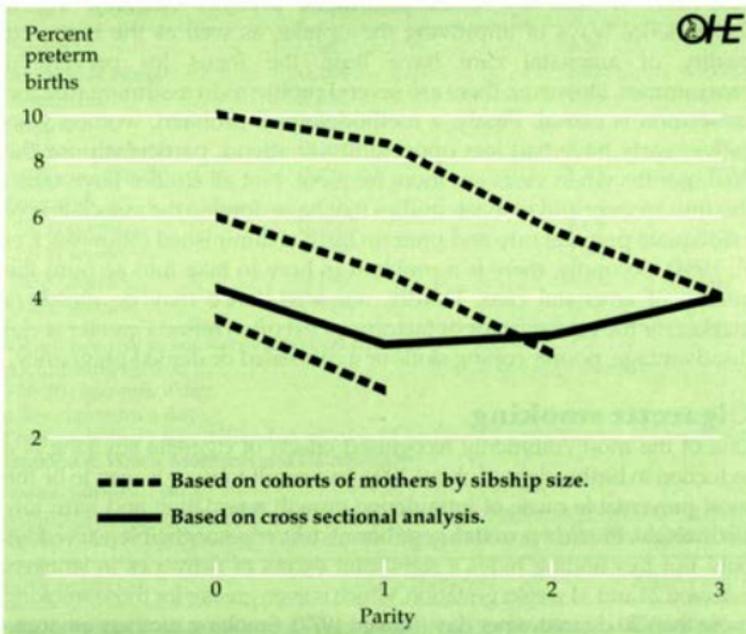
Source: Obstetric and Neonatal Report, Tasmania and published tables.

over-represented among very low birthweight births (2.3 per cent compared with 1.0 per cent of white infants) as they are in all preterm low birthweight births (6.8 per cent compared with 3.0 per cent for white infants) (Kessel & Berendes, 1984).

Not only have the social and demographical associations usually been analysed for all preterm births regardless of the degree of prematurity, but they have also failed to distinguish between elective, complicated and spontaneous preterm delivery. In considering the risk factors for and the causes of preterm birth the three groups of preterm delivery should be considered separately since they are likely to have different aetiological and management implications. For most purposes it will be possible to distinguish between uncomplicated preterm labour and that complicated by, for example, antepartum haemorrhage. In addition, singleton and multiple pregnancies must be considered separately.

Some of the classic epidemiological findings have been updated since information has become available from sets of consecutive pregnancies in the same woman. Cross-sectional studies, in which all first births, all second births and so on were combined showed that preterm delivery was higher in first than second births and then rose at later parities. Figure 3 demonstrates that this U shaped relationship is an artefact and that preterm delivery rates fall with increasing parity in sibships of two, three and four singleton birth (Bakketeig & Hoffman, 1981). Whilst the data from this study, conducted in Norway, did include induced labours, the findings have been confirmed in a study conducted in Aberdeen in labours of spontaneous onset only (Hall, 1985).

Figure 3 Preterm delivery rates in sibships of two, three and four pregnancies



Source: Baketeig & Hoffman, 1981.

Longitudinal studies have supported and extended the earlier analyses which found preterm delivery rates to be increased after a previous preterm delivery or other poor reproductive outcomes. For each birth which is not preterm, the risk of a subsequent preterm birth decreases (Carr-Hill & Hall, 1985). The degree of immaturity of the first born infant is a predictor of the gestation at delivery of the subsequent infant, the effect being most marked when the first birth took place before 28 weeks (Hoffman & Baketeig, 1984).

Newer ideas and mechanisms

Social disadvantage and socioeconomic status, in themselves are not explanations of preterm births but rather are indicators for further investigation. Social class differences include factors such as control over personal, family and social resources and social standards (Lumley, 1987a) as well as the more obvious class differences of financial security, good quality housing and good nutrition.

Antenatal care

Failure to attend for antenatal care early or to attend frequently enough has been consistently associated with preterm delivery. As a consequence ways of improving the uptake, as well as the type and quality of antenatal care have been the focus for prevention programmes. However, there are several problems in assuming that the association is causal. Firstly, a methodological problem, women who deliver early have had less opportunity to attend, particularly for the final months when visits are more frequent. Not all studies have taken this into account and in those studies that have done so the association of inadequate prenatal care and preterm birth is diminished (Showstack et al, 1984). Secondly, there is a problem in how to take into account the quality of antenatal care. Thirdly, non-attendance may be merely a marker for the causal factor or factors since it often reflects greater social disadvantage, poorer coping skills or a concealed or denied pregnancy.

Cigarette smoking

One of the most commonly recognised effects of cigarette smoking is a reduction in birthweight of about 200g, as a result tobacco is seen to be the most preventable cause of intrauterine growth retardation and term low birthweight. Its effect on mean gestation at delivery is negligible, a few days only, but this finding hides a significant excess of deliveries in smokers between 24 and 34 weeks gestation, which is even greater for those smoking more than 20 cigarettes per day (Meyer, 1977). Smoking mothers are more prone to pregnancy complications such as placenta praevia⁴, abruptio placentae⁵ and premature rupture of the membranes. All three are precursors of preterm birth. Table 6 illustrates the relative and attributable risks of smoking for preterm delivery in six studies which suggest that 10-15 per cent of preterm births can be attributed to this factor. The effect is greater for the most preterm births (less than 31 weeks) and a dosage effect is also apparent. When the same analysis is carried out for birthweight instead of gestation (see Table 7), large relative and attributable risks are seen for two birthweight groups: those between 2000 and 2500g, the typical and expected group of growth retarded babies and those less than 1000g, almost all of whom are extremely preterm.

Smoking exemplifies the interconnections between different sorts of risk factors, for example it is strongly associated with social disadvantage, especially during pregnancy.

4 Placenta praevia – describes the position of a placenta which is close to or overrides the outlet (cervical canal) for the uterus.

5 Abruptio placentae (accidental haemorrhage) – separation of part of the placenta from its attachment to the wall of the uterus. May cause tenderness of the uterus, onset of uterine contractions and bleeding. May reduce oxygen supply to fetus.

Table 6 Preterm birth and smoking: relative and attributable risk

<i>Study</i>	<i>Proportion of smokers</i>	<i>RR</i>	<i>AR</i>
Cardiff	0.465	1.36	14%
England & Wales	0.274	1.47	11%
Montreal	0.432	1.38	14%
Ontario	0.435	1.36	14%
California (white)	0.402	1.10	4%
California (black)	0.338	1.25	8%
Tasmania			
22-31 weeks	0.156 ^a	1.65	15%
22-31 weeks	0.049 ^b	2.30	
32-37 weeks	0.156 ^a	1.44	9%
32-37 weeks	0.049 ^b	1.55	

RR relative risk in smokers compared with non-smokers.

AR attributable risk.

a 20-30 cigarettes a day.

b 30+ cigarettes a day.

Preterm delivery was defined as <38 weeks for Cardiff and Ontario; <37 weeks for England & Wales, Montreal and California.

Source: Lumley, 1987a.

Table 7 Low birthweight and smoking: relative and attributable risks

<i>Birth weight (g)</i>	<i>RR (per cent)</i>	<i>AR (per cent)</i>
<1000	2.27	21
1000-1499	1.43	8
1500-1999	1.12	2
2000-2499	2.21	27

RR relative risk in smokers compared with non-smokers.

AR attributable risk.

Source: Lumley, 1987a.

Alcohol and substance abuse

There is considerable disagreement about the effects of alcohol on preterm delivery: one retrospective case-control study found a three fold increase in preterm birth among women drinking two or more standard drinks per day (Berkowitz et al, 1982); one population study could find no effect (Lumley et al 1985b) and a hospital based US study detected an association of shortened gestation with alcohol consumption before but not during pregnancy (Hingson et al, 1982). The adverse effects of alcohol on fetal growth are indisputable for consumption at or above two glasses a day but individual studies and reviewers have been unable to agree about the frequency or existence of ill effects at lower consumption levels (Stein & Kline, 1985; Committee to Study the Prevention of Low Birthweight, 1985).

Drug dependency (opiates and other illicit substances) is a risk factor for both preterm birth and intrauterine growth restriction (Committee to Study the Prevention of Low Birthweight, 1985). The pharmacological effects of these drugs are often exacerbated by cigarette smoking, lack of antenatal care and a disrupted social environment.

Nutrition

Whilst in theory, nutrition might be an important causal link between social disadvantage and preterm delivery or growth retardation neither nutritional intake studies nor experimental nutritional intervention studies have been able to show a reduction in preterm deliveries with improved nutrition (Kristal & Rush, 1984). In fact, high protein supplementation has been found in several studies to increase the chances of very preterm delivery and neonatal death (Rush, 1982).

The effects of maternal nutrition on intrauterine growth retardation are not easily assessed partly because it is not easy to separate this factor from other socioeconomic ones and, more importantly, because of the complicated relationship of pre-pregnancy weight and weight gain during pregnancy. Poor nutritional status before pregnancy and inadequate consumption during pregnancy probably have a small negative impact on fetal weight gain and slightly increase the risk of giving birth to a term low birthweight infant (Committee to Study the Prevention of Low Birthweight, 1985).

Work and physical activity

Regular, moderate physical exercise (swimming, walking and cycling) has been associated with a three fold reduction in preterm delivery rates in the only case-control study to investigate this factor (Berkowitz et al, 1983). Strenuous exercise (jogging, track running and gymnastics) was unusual in both cases and control groups but was more common in the former. The apparently protective effect of moderate exercise may simply reflect the self selection of a particularly healthy sub group, though the effect persisted even after taking into account socio economic status, gravidity, maternal weight, complications of pregnancy and previous history of preterm delivery. The effect of moderate or strenuous exercise during pregnancy on intrauterine growth retardation in the absence of other factors remains unknown.

The relationship, if any, between maternal work in pregnancy and preterm delivery is another possible causal mechanism for the observed association between social disadvantage and poverty.

Unfortunately the many problems of comparing outcome between employed and unemployed women have rarely been given adequate attention. Comparisons frequently take no account of the work involved in housework and childcare; fail to separate those women who are expecting their first child who are mainly in paid employment and those women who already have one or more children who are often at home; and group together in one category all working women regardless of occupation or level of physical effort required for the job.

Heavy physical work combined with a low calorie diet has been shown to result in a lowering of birthweight (Tafari et al, 1980). But apart from this African study, the effects of strenuous work, or work late in pregnancy, or lack of help at home in late pregnancy on intrauterine growth retardation have been inconsistent (Garcia & Elbourne, 1984).

Psychosocial stress

A number of studies have been conducted to determine the influence of psychosocial stress on the incidence of preterm delivery. Standardized questionnaires have been designed to measure perceived levels of anxiety and depression along with a record of recent life events. Some of these earlier studies were performed in retrospect - interviewers visited the women after a preterm delivery (Newton et al, 1979). This was a major criticism of their method, since women who have had an adverse outcome tend to seek a cause (Brown & Harris, 1978). A classic example of this was a study by Stott (1958), which showed that mothers who had delivered a Down's syndrome baby had experienced more shocks than mothers with normal children. It was two years later that the first report linking Down's syndrome and chromosomal abnormality appeared!

However, a recent prospective study has confirmed that there is a significant association between the experience of major life events in pregnancy such as divorce or bereavement and preterm delivery (Newton et al, 1984), but the mechanism by which psychosocial stress precipitates labour is unknown. However, the significance of major life events may be difficult to measure as independent variables.

MEDICAL PROBLEMS OF THE PRETERM BABY

Prior to the 1950s the care available to the preterm infant was limited to warmth and feeding by mouth. Oxygen therapy for respiratory distress was introduced in the 1950s. Unfortunately, at this time the risks of high oxygen concentrations were not appreciated and there were consequently babies blinded as a result of retinal damage. Since then oxygen therapy has been more stringently controlled (see page 28). In the 1960s nasogastric feeding was introduced, improved electronic monitoring became available, and the first attempts at artificial ventilation were undertaken. By the 1970s umbilical catheterisation was routine and micro methods were available which permitted many biochemical tests to be performed on minute samples of blood (Wyatt & Spencer, 1992).

Since then, major advances in the care of the preterm infant have included improved techniques for mechanical ventilation, the introduction of total intravenous feeding, transcutaneous monitoring of blood gases and the widespread use of cranial ultrasound as a monitor for brain injury. Exogenous surfactant therapy for the treatment and prevention of respiratory distress syndrome is currently undergoing clinical trials and preliminary results would suggest that it will make a substantial contribution to the care of preterm infants (see page 25).

The care of the extremely preterm infant should commence prior to birth with skilled obstetric management. If the mother is at a hospital without adequate obstetric and neonatal facilities, transportation to a specialist perinatal centre will probably be necessary. Post-natal transfer of the preterm infant may be necessary but the infant is most safely transferred in utero by transportation of the mother to the specialist centre prior to delivery.

A paediatrician and wherever possible a neonatal nurse attend the birth to provide optimal care from the moment of delivery. The baby is delivered into warmed blankets and dried rapidly. If there is any delay in establishing respirations endotracheal intubation is performed and positive pressure ventilation commenced. Intravenous access is established, the infant is stabilised and then transferred to the neonatal intensive care unit in a specially designed incubator.

Most extremely preterm infants require mechanical ventilation, although occasionally some infants can breathe without assistance. The period of lung ventilation may range from a matter of hours to several weeks depending upon the degree of lung immaturity and the

severity of resultant lung problems (see page 24). In some infants the lungs are so immature that irreversible lung damage occurs leading ultimately to death despite respiratory support. However, in the majority of infants the lungs slowly improve with mechanical ventilation, and the amount of respiratory support is gradually reduced until the infant is able to breath on its own.

Most extremely preterm infants will require full scale intensive care for some weeks after delivery. Following this, less intensive support will be needed for a longer period while the infant grows. Most babies will remain in hospital until they approach their expected date of delivery, for example, a baby born at 24 weeks gestation is likely to remain in hospital for at least 16 weeks before being discharged home.

Infants who are delivered preterm are at risk of various disorders which may complicate their neonatal and subsequent development. The majority of these clinical problems are potentially preventable or treatable. Failure to apply appropriate therapy may, however, be fatal or permanently damaging. Optimal management of preterm infants, whilst difficult and complex, is often very effective.

The many physical and biochemical problems of the moderately preterm infant, that is those born between 32 and 36 weeks gestation, are readily dealt with. These infants comprise approximately five per cent of all live births and account for about 15 per cent of all neonatal deaths (Yu, 1987). In this group of babies, prematurity-related deaths may sometimes occur from severe hyaline membrane disease (respiratory distress syndrome) (see page 24) or infection. Very preterm infants, less than 32 weeks, comprise only one per cent of live births but account for approximately 45 per cent of neonatal deaths. It is now possible with neonatal intensive care to achieve good results with almost all those born at 29 weeks to 31 weeks gestation. However, those extremely preterm infants born at 23 to 28 weeks gestation remain at high risk of death or disability. Although their outcome is improving with better understanding of their pathophysiology and modern technological and therapeutic advances.

The many complex and interrelated clinical problems of the preterm infant, particularly those born at the very early gestations are discussed in the following sections.

Temperature control

Temperature control is by far the single most important post-natal factor determining the intact survival of the preterm infant (Fleming, 1985). In the preterm infant all normal responses to heat (vasodilation

and sweating) and cold (vasoconstriction and increased heat production) are reduced, the responses decreasing as gestational age decreases. Growth retarded infants have normal responses if born after 37 weeks gestation. All low birth weight infants have large surface areas relative to their body mass, little subcutaneous fat and poor glycogen reserves so that they rapidly lose body heat unless proper precautions are taken. Hypothermia⁶ causes 'cold stress' and although the baby tries to maintain body temperature by using up more oxygen and energy resources, often he does not succeed. Even mild 'cold stress' results in a marked rise in oxygen consumption, for example a 2°C reduction in the effective ambient temperature below that of thermal neutrality (33° to 31°C) results in a doubling of oxygen consumption in the healthy term infant. In the preterm infant, in the absence of established respiration such an increased demand would lead to hypoxia⁷ and acidosis⁸. The increased energy expenditure might lead to hypoglycaemia⁹, and in the longer term, increased weight loss or slower weight gain. The risk of sepsis¹⁰ and haemorrhage¹¹ are also greatly increased by significant cold stress (see Table 8).

Table 8 Adverse effects of cold stress

Increased oxygen consumption	—————▶	Hypoxia and acidosis
Increased energy expenditure	—————▶	Hypoglycaemia Increased early weight loss Slow or delayed weight gain
Increased risk of sepsis and haemorrhage		
Increased capillary permeability	—————▶	Hypovolaemia ¹² and increased blood viscosity
Decreased surfactant production		
Neonatal cold injury		
Increased mortality		

Source: Fleming, 1985.

6 Hypothermia – Body temperature below 35°C.

7 Hypoxia – Abnormally low tissue oxygen level.

8 Acidosis – The situation in which there is an abnormally high level of acid in the blood due to a failure to excrete carbon dioxide through the lungs, or due to an accumulation of acid products of cell metabolism when the body cells are receiving insufficient oxygen.

9 Hypoglycaemia – Abnormally low blood oxygen glucose level.

10 Sepsis – Bacterial infection.

11 Haemorrhage – Bleeding.

12 Hypovolaemia – Low blood volume.

Water is lost from the skin by two routes - secretion of sweat via the sweat ducts and passive diffusion of water through the epidermis (transepidermal water loss). Babies born before 36 weeks gestation are unable to sweat in the early neonatal period so that all skin water loss is through the epidermis. Very preterm infants can lose a lot of water through their very thin skins, and evaporation cools them rapidly. Each millilitre of water which evaporates from the skin removes 560 calories of heat (Rutter, 1989). The baby below 1000g is already at a major disadvantage because of his high surface area to weight ratio, so that heat loss by all channels is high relative to heat production. A high transepidermal water loss will render the very immature infant susceptible to hypothermia. For example, in the delivery room, body temperature can drop by 1°C every five minutes despite the provision of supplementary heating.

The very immature infant nursed naked in an incubator can only be kept warm if measures are taken to reduce the high transepidermal water loss. A high ambient temperature of close to 37°C will be necessary. Although water loss can be reduced by as much as 75 per cent by using a waterproof covering such as a plastic thermal bubble wrap (similar to that used to wrap fragile objects) as well as reducing heat loss by convection and radiation, they impair observation of the infant and frequently have to be removed for access. This results in episodes of very high transepidermal water loss.

In practice the only effective method of reducing water loss is to increase the ambient humidity (Rutter, 1989). It is otherwise impossible to avoid hypothermia. It would require an ambient temperature in excess of 40°C to maintain a normal body temperature in a very small and immature infant without the use of humidity. For health and safety reasons such a temperature is not permitted in the UK. The main concern about incubator humidification is a possible increased risk of bacterial infection, particularly as a result of water-borne organisms. This risk can be reduced with proper maintenance and management of the humidifier. However, the risk of infection is a real one and consequently it is recommended that use of humidification be confined to those infants who need it (infants less than 30 weeks gestation for the first week of life) and should not be extended to all preterm infants nursed in incubators. Another possible danger of the use of high humidity is overhydration, with an increased incidence of patent ductus arteriosus¹³.

13 Patent ductus arteriosus – the state of the blood vessel between the pulmonary artery and aorta where it remains open, after it should have closed.

Respiratory problems

Neonatal respiratory distress syndrome (RDS) is a condition caused by pulmonary immaturity, affecting approximately 10 per cent of infants born at less than 37 weeks gestation (Dechant & Faulds, 1991). It is characterised by tachypnoea¹⁴, expiratory grunting, cyanosis¹⁵ and intercostal retractions¹⁶. Risk factors for the development of RDS include preterm birth, male sex, delivery by caesarean section, second born twins and maternal diabetes mellitus (Harvey, 1985; Joint Working Party of the BAPM & RCP, 1992). RDS occurs in the majority of babies weighing less than 1000g. In a recent study (Morley, 1987) with 62 babies under 1000g, 61 required resuscitation at birth and 58 subsequently needed artificial ventilation and increased inspired oxygen. Four were very small for dates; in those who were an appropriate weight for gestational age 95 per cent developed respiratory failure. A third of the babies died and the survivors required mechanical ventilation for an average of two weeks and additional oxygen for 35 days.

The principal feature of this disease is a deficiency of endogenous lung surfactant caused by pulmonary immaturity. Surfactant is a foamy liquid produced naturally in human and animal lungs. It reduces the surface tension between the wet lung tissue and dry air to keep the tiny air sacs in the lungs, called alveoli, from collapsing between breaths. In the absence of adequate surfactant the infant requires increasingly higher inspiratory pressures to re-expand the alveoli and achieve adequate gas exchange. As the infant tires, progressive pulmonary failure develops.

Mechanical ventilation has reduced the mortality from this condition and the incidence of late disabilities (Mayes et al, 1985). Although some survivors have bronchopulmonary dysplasia¹⁷, almost all those with more subtle pulmonary function abnormalities return to normal by 1 year and abnormal respiratory function at school age is an infrequent occurrence (Stahlman et al 1982).

There is strong evidence to suggest that the incidence of RDS can be reduced by at least two prophylactic measures: by giving corticosteroids to women who are expected to deliver preterm; and by giving surfactant to babies judged to be at high risk of developing RDS. Prenatal

14 Tachypnoea – rapid breathing rate.

15 Cyanosis – condition in which the skin, lips, and nails appear bluish due to reduced level of oxygen in the blood.

16 Intercostal retractions – the drawing in of the muscles that lie between the ribs.

17 Bronchopulmonary dysplasia – a disorder of the lung resulting in an increased oxygen requirement and breathing difficulty which may be present for a prolonged period. Associated with a past need for mechanical ventilation.

glucocorticoid therapy, when given to the mother at least 24 hours before delivery of a preterm infant, reduces infant mortality and the incidence and severity of RDS (Crowley, 1989). Other complications of preterm birth (patent ductus arteriosus, intraventricular haemorrhage¹⁸, and necrotising enterocolitis¹⁹) are likewise decreased (Ballard et al, 1992), and a lower incidence of chronic lung disease²⁰ has also been reported (Van Marter et al, 1990). It is believed that the administration of glucocorticoids to the mother may stimulate the production of surfactants by the infant.

An alternative approach to treatment is surfactant replacement therapy after the birth of the infant. Commercially prepared surfactants replace the missing natural lung surfactant until the infant can produce his own a few days after birth. Surfactants are passed down into the infants lungs via ventilator tubes. They may be given either as 'rescue' treatments to infants who have already developed RDS or prophylactically to infants at risk. In either case, studies show that surfactants reduce RDS deaths by about 50 per cent and also reduce the time infants need to spend on ventilators which clearly has important implications for neonatal intensive care costs.

Whilst initial results from clinical trials are promising there remain several questions which have yet to be answered. The first is whether one type of surfactant is more effective than another. There are both natural surfactants (derived from cow, calf and pig lung) and synthetic compounds and comparison studies are being undertaken. A further question to be answered involves the timing of the first dose of surfactant, termed 'preventive' if given soon after birth or 'rescue' if given after the infant shows signs of respiratory distress. A study by Kendig et al (1991) using exogenous calf lung surfactant found significant advantage to the administration of the initial dose of surfactant as prophylaxis rather than as rescue therapy in 479 infants of less than 30 weeks gestation. Other studies have found no differences in outcome between these two approaches (Jung et al, 1991; Dunn et al, 1990). A surprising finding of a study by Vaucher et al (1990) was that there was some advantage in rescue over prophylactic therapy in terms of respiratory or neurodevelopmental outcomes (or both) at 10 to 15 months of age. Clearly more research needs to be done in this area.

18 Intraventricular haemorrhage - bleeding into cerebral ventricles.

19 Necrotising enterocolitis - inflammation of a section of intestinal wall following damage of the lining, often associated with a period of impaired blood flow. The abdomen may be distended and blood is passed in the stools. Air penetrates the wall of the digestive tract and occasionally the gut may perforate.

20 Chronic lung disease - defined clinically as a continuing requirement for supplemental oxygen at 28 days of life.

The problem with administering surfactant as soon as possible after birth, as advocated by Kendig et al (1991), is that 40 to 60 per cent of the infants will have to be intubated and treated unnecessarily. The argument for this approach was based on the assumption that the delivery of surfactant to the airspaces would proceed more effectively before the first breath was taken, and barotrauma²¹ could be avoided. The study by Kendig et al and other studies indicate that there is no substantial advantage in treating infants born after 26 weeks gestation and it remains to be determined whether treating a large number of infants who do not actually require therapy is advisable.

Central nervous system injury

During the first weeks of life the brain is scanned repeatedly by ultrasound to look for evidence of periventricular haemorrhage²² or hypoxic-ischaemic injury²³, the two major causes of brain injury in the preterm infant. The likelihood of neurodevelopmental disability can now be estimated with a reasonable degree of accuracy from the ultrasound appearances of the brain (Stewart et al, 1987). However, whilst satisfactory or adverse neurodevelopmental outcomes for very preterm infants can be reasonably predicted from the results of ultrasound brain scans in the neonatal period, measures of cognitive functioning have been found to be unreliable before four years of age (Stewart et al, 1989) and conditions such as cerebral palsy may not always be accurately diagnosed until that age (Nelson & Ellenberg, 1982).

Periventricular haemorrhage

Minor degrees of haemorrhage are frequently observed but they are now thought not to be associated with significant brain injury or long term disability. Unilateral major haemorrhage involving the brain parenchyma²⁴ is nearly always associated with permanent brain injury and long term disability, especially cerebral palsy, although cognitive development is frequently relatively normal. Bilateral

21 Barotrauma. – Disturbance of function due to difference of barometric pressure on two surfaces of vital organs.

22 Periventricular haemorrhage – Bleeding around the ventricles or cavities within the centre of the brain. This form of bleeding is common in preterm babies and may lead to permanent brain damage.

23 Hypoxic-ischaemic injury – damage to the brain caused by shortage of oxygen and blood supply. This may occur before, during or after birth.

24 Parenchyma – the solid tissue of the brain (as opposed to the ventricles which are fluid filled cavities in the centre of the brain).

parenchymal haemorrhage is associated with such severe brain injury that the outlook is very poor.

Hypoxic-ischaemic haemorrhage

Hypoxia-ischaemia is the most common cause of severe brain injury in survivors of neonatal intensive care. Unfortunately, during the first weeks of life the ultrasound appearances may be normal despite the presence of serious hypoxic damage. It is only at a later stage that periventricular leukomalacia²⁵ or loss of brain tissue leading to ventricular enlargement are seen on ultrasound. As a result of this delay evidence of brain damage may not become apparent until after the infant has left the intensive care unit.

In the near future, using new non-invasive techniques such as near infrared spectroscopy and magnetic resonance spectroscopy, it should be possible to give an accurate assessment of the degree of brain damage within a few days of birth and the likely outcome (Wyatt et al, 1989). Using cranial ultrasound it is already possible to predict longterm outcome with moderate accuracy while the infant is still undergoing intensive care. In the future the accuracy of early prediction should improve dramatically. How this information should be used in clinical decisions about intensive care and the management of the preterm infant is clearly an important ethical issue (see page 39).

Better understanding of the mechanisms of hypoxic-ischaemic brain injury has raised the possibility of effective cerebroprotective therapy. New therapeutic agents which will protect the neonatal brain from injury even when given after an hypoxic insult, may shortly become available (Thiringer et al, 1987). It is possible that this medication could be supplied to the fetus via the maternal circulation prior to delivery, in order to protect the fetal brain. Improvements in the techniques of management of preterm labour, delivery and intensive care, together with new cerebroprotective agents may lead to a significant reduction in the incidence and severity of hypoxic ischaemic brain injury (Wyatt & Spencer, 1992).

Major neurodevelopmental impairment in survivors

Significant disability in extremely preterm survivors is almost entirely due to central nervous system injury. Whilst other organs such as the lungs and kidneys frequently suffer severe damage in the neonatal period permanent impairment of function is rare due to their capacity for growth and regeneration.

25 Periventricular leukomalacia – damage to the area of brain tissue surrounding the cerebral ventricles caused by shortage of oxygen and blood supply to the brain.

Central nervous system damage in preterm infants may lead to one of the four following forms of long term impairment: motor impairment; cognitive and learning disorders; visual impairment; and hearing impairment.

Firstly, motor impairment, that is cerebral palsy. This may range in severity from the mild, causing minimal disability and allowing a virtually normal lifestyle to severe quadriplegia, resulting in the child being totally dependent on others for mobility, feeding and other basic functions.

Secondly, cognitive and learning disorders. These have a wide range of severity but whilst they are frequently of a relatively minor nature they often cause important educational problems. Learning disorders may be isolated to one particular area, such as dyslexia, or global, effecting every area of cognitive development. Fortunately, profound global developmental delay is rare in extremely preterm survivors (Wyatt & Spencer, 1992). Delay in speech development appears to be relatively common but is generally fairly mild. The educational implications for these children and the associated costs will be considered later in the paper (see page 46).

Thirdly, visual impairment. This may be due to retinopathy of prematurity or to injury to the central visual pathways. Retinopathy of prematurity was first described in 1942 and in the following decade it occurred predominantly in modern nurseries raising the suspicion that it might be an iatrogenic disease. In 1956 one of the first randomised, multicentre trials ever performed demonstrated that if preterm babies who did not have lung disease breathed oxygen at a concentration higher than 50 per cent for four weeks, their risk of retinopathy increased three fold (Kinsey et al, 1956). It has been estimated that in that decade close to 10,000 preterm infants worldwide lost their sight because of oxygen therapy (Silverman, 1980). Following the publication of the 1956 report the incidence of retinopathy of prematurity fell to nearly zero but the restriction of inspired oxygen to no more than 40 per cent appears to have resulted in increased morbidity and mortality from lung disease that was reversed only in the late 1960s when measurements of blood gases became available to guide oxygen therapy (Phelps, 1992).

With the development of neonatal intensive care units in the 1970s the survival rates for extremely preterm infants increased and retinopathy of prematurity reappeared. Obviously, excessive use of oxygen was suspected as the responsible agent. However, studies found that continuous monitoring of oxygen levels could not prevent the retinopathy (Flynn et al, 1987; Bancalari et al, 1987). Given the current level of understanding and technical ability, retinopathy of

prematurity appears to be not a preventable disease caused by the misuse of oxygen but rather a disease of prematurity in which any of several factors can injure the retinal vessels (Phelps, 1992).

The fourth form of long term impairment is that of hearing. This commonly takes the form of high tone sensorineural deafness and, when severe, it may require treatment with hearing aids. In addition, secretory otitis media leading to hearing loss has an increased incidence in extremely preterm survivors. Hearing impairment frequently leads to a delay in speech development.

Incidence of neurodevelopmental impairment

As a proportion of all live births of less than 1000g the percentage who survive with a significant neurodevelopmental impairment leading to disability has remained constant over the last 25 years at 5-8 per cent, despite the dramatic improvements in overall survival (Stewart, 1989). This can be compared to the overall disability rate of about 2 per cent in full term infants (Alberman, 1982). As a proportion of extreme preterm survivors the rate of significant disability is about 20 per cent. Thus, whilst the incidence of disability is much higher than for term infants the majority of preterm infant survivors do not have major impairments. Having said this, recent evidence indicates that infants found to be without major impairment at age 1-3 may have learning difficulties at school age, and educational difficulties appear to be relatively common in this group (Stewart et al, 1989).

Although extremely preterm infants have a raised incidence of disability compared with infants born at term, they represent only a small proportion of the burden of handicap in children in the community. One study found that infants born weighing less than 1500g accounted for only 2 per cent of all severely disabled children in the community (Alberman, 1982). Those born at less than 1000g are likely to represent less than 1 per cent of the total. In contrast, the study found that congenital and intrauterine causes of disability, including major chromosomal abnormalities such as Down's syndrome, accounted for 75 per cent of severe disability among children. In England and Wales, approximately 14,000 infants each year will grow to become severely disabled, of these in the region of 280 will have been the results of extremely preterm births (Wyatt & Spencer, 1992). These figures would suggest that due to their relative scarcity surviving extremely preterm infants make only a very small contribution to the burden of handicap within the community.

Other Problems

A few preterm babies develop an inflammation in a section of the wall of their bowel, necrotizing enterocolitis. This causes the abdomen to become distended and the infant may vomit and pass a little blood in the stool. If there is extensive involvement of the bowel, toxins from invading gut germs may cause serious generalised effects and occasionally the wall of the bowel may perforate resulting in peritonitis. Some infants may require surgery for the complications of the condition but many when treated with antibiotics and given adequate nutrition by infusion will recover and be able to tolerate normal feeds again.

Other problems facing preterm infants include heart defects, anaemia, and jaundice.

PREVENTION OF PRETERM BIRTH

Cases of preterm births involving spontaneous uncomplicated preterm labour with a healthy foetus offer the most scope for prevention, although in some cases delivery is already inevitable at the time of hospital admission²⁶. Potential preventive efforts in the uncomplicated group include early identification of preterm labour or its warning signs and inhibition of preterm labour, or, more promisingly, true primary prevention.

Preventive interventions

Cervical cerclage

There are several different surgical techniques for cervical cerclage²⁷ (which will not be considered in this paper) but they all have in common the intention of preventing premature cervical dilation as a factor of preterm delivery. Causes of cervical incompetence include trauma to the cervix during a previous labour, or in association with dilation and curettage, or cone biopsy. It may also occur in conjunction with structural abnormalities related to prenatal exposure to diethyl stilboestrol (Lumley, 1987b), or as an isolated structural or functional congenital abnormality. The rationale for cerclage as prophylaxis from premature cervical dilation or treatment for very early cervical incompetence has never been entirely convincing, even when cervical changes were believed to be a response to uterine contractions. Current knowledge about the cervix makes the rationale even less plausible (Lumley, 1987b) but the procedure is still used.

There is no truly diagnostic test for 'cervical incompetence'²⁸, the decision to insert a cervical suture is most commonly based on past obstetrical history and to a lesser extent vaginal examination. Past

26 Around 60 per cent of preterm deaths are antepartum stillbirths or infants with lethal malformations (King et al, 1985). Even when the infant is alive and not malformed at the onset of labour, some preterm deliveries are elective and others are complicated by maternal or foetal factors, such as bleeding and infection, which contraindicate delaying the delivery (Lumley, 1987). Whether there is a possibility of preventing a proportion of antepartum stillbirths, or elective and complicated preterm births, largely depends on the likelihood of preventing the relevant complications of pregnancy, the success in this area of prevention programmes, particularly the French example will be considered later in this chapter.

27 Cervical cerclage – a stitch placed round the cervix to hold it closed and reduce the possibility of preterm cervical dilation and rupture of the membranes.

28 Cervical incompetence – early opening of the cervix, with consequent bulging of the membranes through it, resulting in repeated mid-pregnancy miscarriages, or preterm births.

obstetric history is not a strong predictor of subsequent early delivery. About 85 per cent of women who have had one previous delivery at 20-36 weeks gestation will carry to term a subsequent pregnancy. Even after two such events the term delivery rate is about 70 per cent (Bakketeig & Hoffman, 1981; Carr-Hill & Hall, 1985).

Difficulties in making a confident diagnosis of cervical incompetence is reflected in the wide variations in the use of cervical cerclage. Rates reported by British obstetricians in a postal survey in 1979 ranged from zero to eight per cent of pregnancies managed (MRC/RCOG Working Party on Cervical Cerclage, 1988). The other reason for this variation is the lack of firm evidence concerning the efficacy of this procedure and the fact that the operation may entail some hazard (Rush et al, 1984; Grant, 1989).

Major but rare complications of this procedure are summarised by Grant et al (1982) as cervical laceration, premature rupture of the membranes, stimulation of myometrial activity²⁹, sepsis, endotoxic shock³⁰, cervical dystocia³¹, cervical stenosis³², uterine rupture, complications of anaesthesia and maternal death. Two common concerns of the procedure are the introduction of infection and the release of prostaglandins during the procedure (Mitchell et al, 1977) which actually increase the risk of preterm birth.

In a multicentre randomised trial of cervical cerclage (MRC/RCOG Working Party on Cervical Cerclage, 1988), 905 pregnant women whose obstetricians were 'uncertain' whether to recommend cervical cerclage, mainly because of a history of early delivery or cervical surgery were randomly allocated to two groups, cerclage or no surgery; 92 per cent were treated as allocated. The results from this trial suggest that the operation had a beneficial effect in one in 20 to 25 cases in the trial. But since the observed differences were not strongly statistically significant and because no such benefit has been found in other randomised trials uncertainty still remains about how much of this apparent benefit is real. This trial is still continuing and hopefully will report more conclusively on the advisability of cervical cerclage.

Antenatal care and bed rest

As mentioned earlier (see page 16), failure to attend for antenatal care early on frequently enough has been associated with preterm delivery, however a causal relationship has yet to be conclusively established.

29 Myometrial – muscle of the uterus.

30 Endotoxic shock – blood poisoning.

31 Cervical dystocia – hole in the cervix too small for foetus (or menstrual flow etc) to pass through.

32 Cervical stenosis – see footnote 31.

Bed rest is sometimes prescribed for pregnant women at high risk of preterm labour. Studies which have been conducted to date have provided little evidence to support this practice as a preventive measure for preterm birth and have in fact lent support to theories about its safety. Current clinical teaching is that women do not and cannot rest at home and it is therefore important to note that the studies so far have all been conducted in hospital (bed rest at home with sufficient practical support has yet to be properly evaluated).

Two controlled trials in Finland and Zimbabwe, the latter employing randomised allocation, have confirmed that bed rest in hospital from 29 (Finland) or 32 (Zimbabwe) weeks is associated with more rather than fewer preterm deliveries (Hartikainen-Sorri & Jouppila, 1984; Saunders et al, 1985). The pooled results of these two studies show that the finding is unlikely to be due to chance, and is concordant with the increase in very low birth weight infants in the bed rest group within both trials, though the trials were not large enough to demonstrate this latter point conclusively (Lumley, 1987b).

Progestogens

As with the interventions mentioned above the use of progestogens is almost always a prophylactic intervention, used in women predicted to be at high risk of preterm delivery. The basis for its use is the role of progesterone in keeping uterine activity to a minimum, though there is little evidence to suggest that progesterone deficiency is a cause of preterm labour in human pregnancy.

Five trials have compared the prophylactic use of progesterone with a placebo (Johnson et al, 1975; 1979; Hartikainen-Sorri et al, 1980; Hauth et al, 1983; Yemini et al, 1985). Three of the studies were carried out in women who were at high risk of having a preterm birth due to previous reproductive history, one in twin pregnancies and one in women believed to be at moderate risk due to the fact that they were in active military service during their pregnancy (see Table 9). These trials have produced rather mixed results largely because they were too small to have the power to exclude either a beneficial or harmful effect. The trial in women with a history of preterm birth or at least two spontaneous abortions did find a significant reduction in preterm labour and birth with progestogen treatment but no difference in the proportion having a live term infant since the treated group also had an excess of late first trimester and second trimester abortions (Yemini et al, 1985). The trial in twin pregnancies detected no beneficial effect of the drug on gestation at delivery, birth weight or perinatal delivery (Hartikainen-Sorri et al, 1980). The active military duty group of

Table 9 Preterm births in trials of progesterone

	<i>Drug</i>	<i>Placebo</i>	
Johnson et al 1975	0/18	11/26	High risk – past history
Johnson et al 1979	5/21	2/6	High risk – past history
Hartikainen-Sorri et al 1980	12/39	9/38	Twins
Hauth et al 1983	5/80	5/88	Active military duty
Yemini et al 1985	5/31	14/37	High risk – past history

women recruited by Hauth et al (1983) were not clinically at high risk. However it is interesting to note that eligible women who refused to take part in the trial had higher rates for preterm delivery (10.2 per cent) than the treated (6.3 per cent) and the placebo (5.7 per cent) groups.

Tocolytic agents (beta-adrenergic agonists)

Use of these pharmaceuticals for the prophylaxis of preterm labour has been documented in two European countries (Keirse, 1984). Prophylaxis is used in women identified as being at high risk of preterm delivery. However, due to the low positive predictive value of risk assessment, by both obstetricians and mothers, most women identified as being at high risk deliver at term. Treating all of these women with tocolytic agents ensures that 'a potential but relatively imprecise risk of preterm birth tends to be replaced by the certain risk of dubious treatment, whose merits are undemonstrated and whose hazards are unknown' (Keirse, 1984).

Pharmacological inhibition of preterm uterine activity with beta-adrenergic agonists has been used extensively in the last 20 years to arrest preterm labour. It has been assumed that use of these agents reduces perinatal mortality and the frequency of long term handicaps by reducing the rate of prematurity.

In a pooled analysis of 16 placebo controlled trials of tocolytic agents (King et al, 1985) it was found that beta-adrenergic agents were effective in reducing the proportion of women who delivered within 24 hours and within 48 hours of treatment. This prolongation of pregnancy was reflected in a reduced incidence of low birth weight (less than 2500g) but the reduction was not statistically significant. There was little evidence that such treatment was associated with a decreased likelihood of preterm birth, a reduction in perinatal mortality or newborn respiratory disorders.

In a recent study (The Canadian Preterm Labour Investigators Group, 1992), 708 women with preterm labour were randomly assigned to receive either an intravenous infusion of either the

beta-adrenergic agonist ritodrine or a placebo. Assignment was made with stratification according to four categories of gestational age (20-23 weeks, 24-27 weeks, 28-31 weeks and 32-35 weeks). The primary objective of the study was to assess the effect of ritodrine on perinatal mortality. Secondary objectives included the extent to which delivery was delayed with ritodrine, the effects on birthweight, maternal morbidity and neonatal morbidity.

This study confirmed the findings of previous studies in so far as ritodrine was not found to have any beneficial effect on fetal or neonatal mortality or on the incidence of preterm delivery but was found effectively to reduce the incidence of delivery within 48 hours after treatment. In the light of the collected evidence it now seems almost certain that treatment with beta-adrenergic agonists significantly reduces the rate of delivery within 48 hours but that this has not led to clinically important reductions in the rates of preterm delivery or low birthweight.

Since the principal effect of beta-adrenergic agonists is to delay delivery for a few days it is important that this time is used effectively. It may be that the time gained could be best used in moving the mother to a unit with facilities available to deal with a preterm infant. Another possible use of this time would be the administration of a course of glucocorticoid therapy. The use of glucocorticoid therapy during preterm labour has been shown to decrease neonatal mortality, particularly from respiratory distress syndrome (see page 00). It is likely that more liberal use of glucocorticoid therapy in conjunction with tocolytic treatment, that delays delivery for 48 hours, would have substantial benefit (The Canadian Preterm Labour Investigators Group, 1992).

It is important that further research is undertaken to determine what other interventions might successfully use the time gained by the use of tocolytic agents to improve perinatal outcome.

Prevention programmes

Most research in the area of preterm birth has concentrated on the question 'why do some women have preterm infants?'. Perhaps a more important question may be 'why do some populations have so many preterm births?'. Differences in preterm birth rates over time (Aberdeen 1950-80, Hall, 1985) or between countries, regions or racial and ethnic groups (Committee to Study the Prevention of Low Birth Weight, 1985) show that the causes, whilst they are unknown, are not inevitable. If we knew with certainty what the causes of preterm birth were it might be possible to control them. The clues must be sought from differences between populations rather than differences

between individuals within a population (Lumley, 1987b) and preventive measures adjusted accordingly.

Smoking reduction

If, as discussed earlier, in the region of 15 per cent of preterm births are attributable to cigarette smoking then interventions to reduce smoking have the potential to reduce preterm delivery as well as improve fetal growth. However, the randomised trials of smoking reduction programmes which have been published have had mixed results and none specifically looked at preterm delivery rates, concentrating on birth weight.

The first trial using physician advice during pregnancy as the intervention was unsuccessful in altering fetal outcome (Donovan, 1977). Other trials using more sophisticated strategies to promote and reward the desired behaviour (Nowicki et al 1984; Windsor et al, 1985) did succeed in encouraging women to stop smoking and in increasing birth weight (Sexton & Hebel, 1984). However, the trial size (Sexton & Hebel, 1984) was not large enough to detect changes in the preterm birth rate especially before 32 weeks when the smoking effect is most likely to be operating. Whilst for reasons of increased birth weight alone it is probably worth adopting such a programme of smoking reduction clearly a larger trial is needed beginning in early pregnancy to assess whether preterm delivery can also be reduced in this way.

The French experience

Support for preterm birth prevention programmes and their widespread implementation rests largely on the special case of France (the programme commenced in 1971 and as an intervention strategy had several points: firstly, to define and analyse the population risk factors; secondly, to apply this risk analysis for preterm delivery to all pregnant women; and thirdly to intervene for prevention by adapted measures to each risk level category (low, medium and high) and to the specific problems). For all women precise information was obtained regarding the relationship between daily life events and/or hard physical work to uterine contractions and a higher risk of preterm birth. For medium risk women it was considered that work leave from a hard job and recommendation to undertake only light domestic chores were the most important contributions. In these cases arrangements were made to meet the cost of compensation for work leave by the national security system, or home help obtained from the city council. For high risk women there were no specific interventions, apart from cervical cerclage. In addition, for all women, there was a modification of the prenatal care given, with earlier booking in and

more frequent prenatal examinations by the specialist obstetrical team rather than the general practitioner.

Reductions in the preterm birth rate, defined as live births before 37 completed weeks gestation have been reported for a teaching hospital (6.46 to 3.76 per cent over 11 years); a region (6.1 to 4.2 per cent over 12 years) and nationally (8.2 to 5.6 per cent over 10 years) (Papiernik, 1984; Papiernik et al, 1985a; 1985b). Similar results have been reported in hospitals and regionally, from Dublin (Boylan & O'Driscoll, 1983) and from Aberdeen (Hall, 1985), although these were over longer time periods.

A summary of the findings in the French regional study is that the reduction in preterm births occurred not among women with classical risk factors (bleeding during pregnancy, previous preterm birth etc) but in women without major complications and giving birth at optimal ages. It was also reported that the classical risk factors themselves had become less common among pregnant women (Papiernik et al, 1985a).

Changes in the entire population appear to have been important in reducing preterm births rather than specific interventions for a particular group. These findings were compatible with the findings of a national reduction in France as a whole. This would suggest that the attention of clinicians and policy makers should be directed towards more general prevention measures such as uptake of antenatal care; public education about occupational fatigue, travel or commuting; the physical stress involved in housework and child care; policy changes on earlier maternity leave or work reduction with income maintenance; home help provisions. The adage that 'a large number of people at a small risk may give rise to more cases of the disease than a small number who are at high risk' is true for preterm birth within a hospital (Main et al, 1985) and for a whole region (Aberdeen: Carr-Hill & Hall, 1985). This situation limits the utility of the high risk approach (Lumley, 1987b).

The future

The success of the French programme in reducing preterm births in the low risk group to such an extent that they were reflected in the national data suggests that a population approach to preterm birth has much to offer. An example of the difference between the high risk and population approach to preventing preterm birth is the case of cigarette smoking. Cigarette smoking is classed as a high risk activity during pregnancy and as mentioned earlier may be responsible for up to 15 per cent of preterm births. However, attempts to change individual smoking behaviour during pregnancy has met with little

success. Few women, and those the less heavy smokers, give up during pregnancy. The population strategy would be to reduce smoking in the whole population using strategies which have been shown to be effective such as taxation, control of tobacco advertising, and banning smoking in public areas. This is comparable to the French public education programme on occupational fatigue in pregnancy and the need for paid leave and provision of household help.

More research is clearly needed in the area of clinical intervention among high risk women but unless social inequality is removed the primary concern should be the discovery and control of the causes of preterm birth within the entire population (Rose, 1985).

ETHICAL AND COST ISSUES RAISED IN PRESERVING PRETERM INFANTS

Neonatal intensive care is an area where hi-tech medicine has been remarkably successful. However, the sophistication of intensive care techniques, the improved ability to detect severe brain damage, and the high cost of neonatal intensive care has raised new ethical dilemmas not only for medical and nursing staff but also health service administrators and government policy makers. In this section the ethical issues raised by the treatment of preterm infants will be considered on two levels: firstly, the relationship between the doctor and the patient (the infant); and secondly as a use of a scarce economic resource. It is not expected that any firm conclusions will be reached but rather that the issues raised will enable the subject to be opened for wider debate.

The doctor and the patient

The birth of an extremely preterm infant in a developed country might be seen simply as an occasion for applying the full range of modern technology available in order to save the infant's life. Whilst this approach is appealing to some of the medical profession because it seems to avoid ethical dilemmas, that is, it allows the doctor to say that he is merely a technician doing everything possible to save a life, it has to be considered whether this view is justified in terms of the individual situation of the infant and the infant's family. Should the saving of life be of paramount importance, regardless of circumstances, irrespective of quality of life of the infant or the effect on the family?

On the individual level, the first and most important question to be raised by the birth of an extremely preterm infant is to what extent it should be treated³³. A decision has to be made whether to offer intensive treatment in the first place and then if the infant's condition should deteriorate a decision must be made whether or not to withdraw treatment. Disagreements about the treatment of some infants, in particular the very low birthweight and early

33 For all preterm infants, regardless of the degree of impairment, there is a minimum level of acceptable care which includes warmth, hydration, analgesia where indicated and nursing care. In infants in whom death is likely to be rapid it may not be necessary to initiate artificial feeding or hydration. However, in infants who are likely to die more slowly some form of feeding or hydration is usually appropriate. It is not generally acceptable to allow an infant to die slowly of dehydration or starvation. The prevention of pain and distress, as in all terminal care, is clearly of paramount importance.

gestation infants, exist partly because of different views of the prospects of such infants but also for ethical reasons, for it cannot be disputed that respiratory support will greatly improve an infant's chances of survival. The problem is that such infants, if they survive, are at serious risk of handicap. Consequently, we reach the first serious ethical dilemma: is human life of value regardless of quality? Should every effort be made to preserve human life irrespective of the risk of serious impairment?

In addition to the future prospects that the infant may have, consideration should be given to the fact that the treatment needed to save the infant's life may be painful for the infant, and unlike a normal adult, the infant cannot choose whether it wishes to undergo treatment. Thus the decision to initiate treatment which may save life should be based not only on the judgement that life should be preserved, despite the risk of handicap, but also on the judgement that the value of preserving the life outweighs the suffering the treatment will cause (Kuhse & Singer, 1987).

Similar questions may recur once treatment has commenced. If the decision is made to put the infant on a respirator what should be done if the baby then suffers a major intraventricular haemorrhage? In many hospitals if it was known that a haemorrhage had occurred before respiration had begun the baby would not have been placed on the respirator. Should the respirator now be turned off? Whilst there is a psychological difference between not commencing respiration at all and disconnecting it once it has begun it is debatable whether there is a moral difference.

It should be clear even from this brief outline of some of the issues that there are a number of questions which must be brought into the open for discussion. Consideration should be given to the following ethical questions: should we preserve human life irrespective of its quality? Is there the same obligation to preserve the life of a newborn infant as there is to preserve the life of an adult? What account should be taken of the likely pain being inflicted on the infant? Whose interests should be taken into account - only the baby's, or those of the family as well? Is there a difference between not starting treatment and withdrawing treatment? Cutting across all these questions is the crucial practical matter of who is to make these decisions.

There are no easy answers to these questions. Ethicists and doctors have long debated the issues involved without reaching any unanimous conclusions let alone establishing guiding principles. However, with the technical ability to save ever younger and smaller babies and increasing pressure on health resources the need for answers to these questions is becoming more urgent.

The cost of saving the preterm infant

Until fairly recently, care for the very small liveborn infants (less than 1500g) in Europe and the United States was to keep them warm, free from infection and fed. This is still the only care available for such babies in many parts of the world. Those that can survive do and high mortality is accepted. The financial costs to a health service of such care is relatively low, as it requires nursing care and very little special equipment. However, with advances in medical intensive care, younger and smaller infants can be sustained and the costs of care have risen.

Costs of hospital care for very low birthweight infants

There have been a number of studies of the hospital costs of caring for very low birthweight infants. Table 10 summarises some of the main results from these studies. Direct comparisons between these studies are difficult. In comparing the results from different centres, it is helpful to know how the total cost was distributed between the different inputs. For example, labour costs are much higher in the United States than in the UK. This may in part explain the differences in the cost per survivor between the two countries. Comparing the costs and benefits of the different programmes is further complicated due to the different time periods used over which the costs and benefits occur. Successful neonatal intensive care has benefits which can occur over the very long term (Mugford, 1988). The relative weight given to the value of events occurring at different times can have a significant effect on the balance of benefits and costs of care for some groups of infants.

In addition, there are variations in methodology; one study (Boyle et al, 1983) attempts to include all categories of hospital cost for all patients served by a regional neonatal care programme, relating to care in a neonatal intensive care unit (NICU) and other hospital wards, until discharge home. Other studies are not so comprehensive, being restricted to an analysis of the costs of care for infants admitted to one neonatal intensive care unit only.

This being said, it is possible to make some general comments. Firstly, the cost per patient day in the NICU is initially high and decreases over time. Secondly, costs borne within the NICU itself account for the majority of the total costs, and within the NICU the largest single category is nursing costs. Thirdly, costs per patient increase rapidly with decreasing birthweight. However, caution should be exercised in using the results of these studies for decision making, since as Sandhu et al (1986) point out the choice of the 1000g division between birthweight groups is arbitrary and there is a

continuum of expected costs with infants who weigh 999g likely to incur costs similar to those weighing 1001g. Fourthly, factors such as whether or not the infant underwent a significant degree of surgery or received more than 24 hours of assisted ventilation were important in explaining the substantial variation in costs per patient (Boyle et al, 1983; Phibbs et al, 1982; John et al, 1983).

Table 10 **Costs of hospital care for very low birthweight newborns**

	N	Birth-weight (g)	Study period	Survival percentage		Cost/Survivor (US\$,000)	
						1000-1499g	1000-1499g
				<1000g	1499g	<1000g	1499g
Los Angeles, California Pomerance et al (1978)	75	<1000	1973-75	40	-	88	-
McMaster, Hamilton, Canada Boyle et al (1983)	265	<1500	1973-77	22 [†]	77 [†]	53	16
Boston, Massachusetts Kaufman and Shepard (1982)	21	751-1000	1977	40	-	26	-
San Francisco, California Phibbs et al (1981)	1185	All weights	1976-78	49*	87*	46	18
Providence, Rhode Island Walker et al (1984)	247	<1000	1977-81	32*	-	43	-
Birmingham, UK Newns et al (1984)	1329	All weights	1980-81	48*	83*	21	11
Westmead, NSW, Australia John et al (1983)	136	All weights	1981	61*	83*	33	16
Liverpool, UK Sandhu et al (1986)	182	<1500	1983	50*	86*	13	6
Cleveland, USA Hack and Fanaroff (1986)	98	<750	1982-85	20 ^{††}	-	159 ^{††}	-

*As percentage of admissions to neonatal unit.

[†]As per cent of births in a geographically defined population.

^{††}Only includes births weighing up to 750g.

Source: Mugford, 1988.

Not only health sector resources are used in caring for low birthweight babies. Economic evaluation should take account of the time and effort of parents and other agencies such as social workers and counsellors (Mugford, 1988). Of the studies given in Table 10 only Boyle et al (1983) measured parent's costs. In a review of the literature, Mugford (1988) was only able to find one other study which measured the costs to parents. Smith and Baum (1983) estimated the financial costs to parents visiting their babies in a regional neonatal unit in Oxford; even for families of inborn babies, travel costs per family of up to £350, with a mean of around £40 were estimated. Of the families included in the study 24 per cent were 'in financial difficulties', and these families tended to have smaller babies with longer stays. The authors did not measure the length of time parents spent in the neonatal unit and the consequent cost that this imposed in lost earnings, nor did they measure costs of caring for other children.

Economic evaluation of regional neonatal intensive care units

The most comprehensive evaluation of regional neonatal intensive care units currently in the published literature is that carried out in Canada by Boyle et al (1983). They evaluated the economic aspects of neonatal intensive care of very low birthweight infants using costs and outcomes both before and after the introduction of a regional neonatal intensive care programme in Hamilton-Wentworth County. The two periods compared were 1964-69 and 1973-77. The data requirements for the study were extensive, including not only the cost data referred to above, but also mortality rates by birthweight group determined at hospital discharge plus data on morbidity, and associated follow up costs, such as use of special services and appliances, and parental care at home.

Health outcomes were expressed in terms of both life years gained and quality-adjusted life years (QALY) gained. The latter were produced using a range of utility values for different health states derived by interviewing parents of school children in the area. These ranged from 1 for perfect health to 0 for dead. However, some states were considered by the parents to be worse than death and the range was extended to -0.39. Hospital costs and long term costs and estimated life time earnings were obtained. Cost effectiveness³⁴, cost

³⁴ Cost effectiveness analysis – compares the effectiveness of two or more programmes of treatment in physical units, e.g. in a comparison of heart and renal transplants the common effect is survival which may be measured as life years gained. By adding the cost of the operation into the equation a cost per life year gained can be calculated.

benefit³⁵ and cost utility³⁶ analyses were performed. A five per cent discount rate to allow for inflation was used.

All measures show a more favourable outcome for the 1000-1499g group compared to the 500-999g group (see Table 11). For infants weighing between 1000-1499g the net economic cost per life year gained through the use of neonatal intensive care was \$1,260 and for infants weighing between 500-999g it was \$10,240 (US dollars, 1983 prices). When utility values were added a cost of \$1,400 and \$24,500 per QALY was derived. It is clear from this that whilst infants weighing between 1000 and 1499g are being valued at 90 per cent of a life year, infants in this study weighing between 500 and 999g were only being valued at around 40 per cent.

Other studies of the regionalisation of care (Walker et al, 1985; McCormick et al, 1985) have confirmed the cost effectiveness of organising care in this way. However, there is some objection to a policy of concentrating neonatal intensive care skills only at regional centres. It has been suggested that skills at outlying hospitals in short term resuscitation and care of very low birthweight babies may alter the effectiveness of transfer arrangements.

Table 11 Measures of economic evaluation of neonatal intensive care according to birthweight class (5 per cent discount rate)

<i>Period</i>	<i>Birthweight class</i>	
	<i>1000-1499g</i>	<i>500-999g</i>
To hospital discharge		
Cost/additional survivor at hospital discharge	83,500	143,800
To age 15 (projected)		
Cost/life-year gained	8,500	17,120
Cost/QALY gained	10,900	56,300
To death (projected)		
Cost/life year gained	4,060	13,100
Cost/QALY gained	4,500	31,400
Net economic benefit (loss)/live birth	(3,650)	(22,600)
Net economic cost/life-year gained	1,260	10,240
Net economic cost/QALY gained	1,400	24,500

Source: Adapted from Boyle et al, 1983.

Values are expressed in 1983 US dollars.

35 Cost benefit analysis – attempts to give an estimate of the financial value of the resources used by a programme of treatment compared to the financial value of the resources the programme might save,

36 Cost utility analysis – attempts to compare the costs and impact upon the utility or the quality of the outcome of different methods of carrying out an activity. This is done using a variety of measurements of health status and then converts them to a measurement which facilitates comparison across a wide range of health care.

The costs of saving very low birthweight infants in the United Kingdom

Using the figures from three studies conducted in three different regional neonatal units (Newns et al (Birmingham), 1984; Sandhu et al (Liverpool), 1986; Ryan et al (Leeds), 1988) it is possible to make some general observations about UK neonatal intensive care costs. Approximately 1 per cent of all births in the United Kingdom are of babies weighing less than 1500g. In 1990 there were 678,040 live births. Of these live births 6,492 weighed less than 1500g (0.95 per cent). In the three aforementioned studies around 73 per cent of infants weighing less than 1500g survived, in national terms in 1990 this would mean that of the 6,492 infants 4,739 survived. However, it is improbable that the national figures are as high as this since not all infants are born in a regional unit and due to pressure for neonatal intensive care places there is likely to be in operation a degree of selectivity of infants. At 1984 prices, the three studies had costs per patient of between £4,159 and £6,979 and costs per survivor of £4,490 and £8,192. If these figures were to be reflected in all regional units the cost to the NHS of neonatal intensive care for infants whose birthweight was less than 1500g, put into 1990 prices, would be between £42 and £70 million per annum.

Whilst compared to the total NHS expenditure, £32,422 million in 1990, the amount spent on neonatal intensive care for low birthweight babies appears slight it is important to consider what opportunities or benefits have been foregone when resources are used for the purpose in question. This measure is referred to as 'opportunity cost'. Where a budget is limited the cost of more spending on one part will be a reduction in the benefits from other uses of the same resources. For example, increased neonatal care resources might mean reduced resources for postnatal support and advice for mothers of healthier babies (Mugford, 1988).

In a study of infants of birthweights less than 1,500g born in 1980 and 1981 to mothers resident in two Mersey health districts (Stevenson et al, 1991) the sum of neonatal costs from birth to first discharge home, post natal costs to the age of four years and projected life-time costs for abnormal children (where applicable) were calculated. The average total cost of a survivor ranged between £146,012 for an infant weighing 700-799g and £7,736 for an infant weighing 1,400-1,499g (1984 pay and prices). Whilst they do not represent the full cost to society, since, for example no attempt was made to measure the socio-economic costs to families, the estimates do account for a high proportion of exchequer costs (for explanation of the methods and costs used in this study see Appendix).

Clearly, caring for very low birthweight babies is expensive and it appears that on average costs increase with decreasing birthweight. Many studies support the view that access to neonatal intensive care facilities improves the chances of survival. The evidence about impairment is less clear, and better data about impairment in populations with and without access to neonatal care would make future evaluations of neonatal care easier (Mugford, 1988).

Research indicates that given efficient referral and transport mechanisms, regional organisation of neonatal intensive care is more cost effective for health care providers than the provision of a full intensive care service in every hospital providing a maternity service. However, as already stated the costs for parents can be very high, particularly transport costs.

The findings of economic studies stimulate considerable concern about the interpretation and use that will be made of the results. In the study by Boyle et al (1983) whilst it is pointed out that the increased cost of care of babies weighing less than 1000g outweighed the improvements in outcome they do not conclude that care of this group is contra-indicated. In fact they highlight the point that many health interventions, such as haemodialysis, are carried out in similar circumstances, thus suggesting that society has decided to pay the account in spite of the net cost.

The purpose of economic analysis is to provide evidence for comparing the benefits of alternative uses of resources. A study by Torrance and Zipursky (1984) shows that intensive care of babies weighing between 1000-1499g and between 500-999g falls well within the range of costs and benefits experienced for other widely accepted health care technologies (see Table 12). It could be argued that for the wealthier countries of the world, where considerable resources are already committed to the health and well being of all pregnant women and their babies, neonatal intensive care is a rational decision.

A recent American study (Chaikind & Corman, 1991) (1987) found that low birthweight survivors were likely to experience serious health problems in infancy and beyond and found that they were more likely to experience preschool developmental delays. They also discovered that children who weighed less than 2,500g were 50 per cent more likely to be enrolled in any type of special education than children of normal birthweight. The authors calculated that, in the US, this results in an incremental cost of special education of \$370.8 million (1989-90) per year due to low birthweight. Whilst the provision of services in the US and the UK are not strictly comparable, if these costs were to be repeated in the UK and adjusted for population size, the cost in the UK for special education for low birth weight children would be in the region of £150 million per annum (1989-90).

Table 12 Comparative cost-utility results for selected programmes*

	<i>Reported cost/QALY* gained in US dollars (years)</i>	<i>Adjusted†† cost/QALY† gained in US dollars 1983</i>
PKU screening	<0 (1970)	<0
Postpartum anti-D	<0 (1977)	<0
Antepartum anti-D	1220 (1983)	1220
Coronary artery bypass surgery for left main coronary artery disease	3500 (1981)	4200
Neonatal intensive care, 1000-1499g	2800 (1978)	4500
T4 (thyroid) screening	3600 (1977)	6300
Treatment of severe hypertension (diastolic >105 mmHg) in males age 40	4850 (1976)	9400
Treatment of mild hypertension (diastolic 95-104 mmHg) in males age 40	9880 (1976)	19100
Estrogen therapy for postmenopausal symptoms in women without a prior hysterectomy	18160 (1979)	27000
Neonatal intensive care, 500-999g	19600 (1978)	31800
Coronary artery bypass surgery for single vessel disease with moderately severe angina	30000 (1981)	36300
School tuberculin testing programme	13000 (1968)	43700
Continuous ambulatory peritoneal dialysis	35100 (1980)	47100
Hospital haemodialysis	40200 (1980)	54000

*These studies use similar, but not identical, methods. Generally, costs are net health care costs; however, discount rates and preference weights are not completely consistent. Differences in methods should be considered when comparing the relative cost-utility. For details, see original sources.

†QALY denotes quality-adjusted life-year.

††Adjusted to 1983 dollars according to the US Consumer Price Index for Medical Source: Torrance and Zipursky, 1984.

However, even if it were to be agreed that it is economically acceptable to provide neonatal intensive care for all low birthweight babies, questions still remain about the ethics and morality of such action when the risks of a lifelong impairment or a parental breavement after 'bonding' with a preterm infant are taken into account.

CONCLUSION

Modern methods of neonatal intensive care have been remarkably successful in two ways. First, the risk of death in very low birthweight infants has now been greatly reduced. And, second, the chances of normal undamaged good health for less extremely preterm infants has greatly improved. Ironically, the effects of these two advances have to some extent offset each other. The greater vulnerability of new survivors counterbalances the reduced risks for less extremely preterm infants. This continuing trend must be a cause for both social and economic concern.

Over a fifteen year period, between 1968 and 1983, during which time the chances of a very low birth weight baby being born alive and surviving to the end of the neonatal period improved from 35 to 58 per cent, there was an increase in hospitalisation in the first two years of life for this group from 22 to 44 per cent (Mutch, 1987). Much of this rise can be explained by changes in the practice of hospitalisation of the child population as a whole but set against admission rates of around 10 per cent for the total infant population it can be seen that there is considerable excess morbidity in this group.

Very low birthweight infants do not contribute greatly to the total demands on hospital use because their absolute numbers are small in relation to the whole child population. However, for the individual unit manager these infants can be a problem and sometimes an embarrassment since unlike specific operations or procedures the number of preterm births that a unit might be expected to deal with at any given time cannot be precisely estimated and easily budgeted for. In addition, their demands are increasing and they do stay in hospital longer than their heavier contemporaries. These infants often require more specialised care for relatively simple procedures, like hernia repair, because of co-morbidity such as impaired lung function which is a consequence of their initial immaturity.

Information about the outcome of very low birthweight infants in the longer term is important in terms of assessing the effectiveness of neonatal intensive care and has been the focus of considerable research activity. Such information is useful in the process of decision making about the allocation of resources both to neonatal intensive care and to the care of those children who survive impaired. The search for readily available and manageable indicators of the effectiveness of neonatal intensive care, however, apart from survival, has proved elusive. The results from long term follow up are clearly not available until some time after the perinatal events they reflect. Studies in large geographically defined populations are often

cumbersome to manage and expensive to mount: by their very size, they cannot do more than act as a wide gauge to identify severely impaired children and often do not provide detailed information on minor problems. Smaller, in depth studies serve to inform local perinatal services but can rarely be successfully extrapolated to other populations.

Ideally, routine child health surveillance systems should be able to provide the kind of information needed to evaluate the effectiveness of neonatal intensive care and as surveillance systems are developed nationally this information should hopefully become available.

Medical advances in neonatal intensive care have presented society with a dilemma. The ability to ensure the survival of increasingly lower birthweight infants and the decision to do so (occasionally the failure to make a decision not to act) must be weighed against the resultant increase in the numbers of impaired children, their expected quality of life, and the socio-economic consequences for the community as a whole. Consideration should be given not only to the resources expended in preserving the infants and their continued care but also to the loss of these limited resources to other areas of health care need.

Perhaps resources would be more effectively used if directed towards research into the causes and ultimately the prevention of preterm birth. Research is currently being undertaken in this area and the results of these studies will be important in determining future policy.

As previously discussed, as yet, the factors affecting preterm birth are complicated and not fully understood. Comprehensive care is required to reduce the rate of preterm birth since it is only through a programme such as that adopted in France (see pages 36-37) that the interrelated environmental, behavioural, biological, clinical and other factors can be systematically addressed. The population approach to prevention of preterm birth has much to commend it; many of the components of prevention programmes such as antenatal care often miss those women at highest risk of a preterm birth, like teenagers and socially disadvantaged groups. The difficulties in eradicating social inequality underline the importance of more research to establish the causes of preterm birth and in understanding the causes to work towards reducing the incidence.

APPENDIX

Predicting costs and outcomes of neonatal intensive care for very low birthweight infants

Methods: Outcomes

The geographically determined sample comprised all infants of BW less than 1.500g born in 1980 and 1981 to mothers resident in two Mersey Health Districts. It was a sub-set of a larger population which has been reported previously. There were 109 VLBW infants, all of whom were treated in the Regional NIC Unit. Mortality was 37 per cent, and the 69 survivors were followed up and assessed at the age of four years. Disabilities were classified on a 4 point scale as follows: mild (class 2), moderate (class 3) and severe (class 4). Normal children were allocated to category 1. Expected life span was assumed to be 70 years for all except the severely abnormal children in category 4 for whom it was reduced to 45 years.

Disabilities were detected in 11 (16 per cent) of the children. Three were classed as mild; one was moderate and seven were severe. Table 1 shows the number of infants, survivors and their disabilities in 100g BW ranges. The final column of Table 1 gives the number of quality adjusted lives (QALs) produced. This was calculated by allocating a quality adjustment coefficient to disabled children according to the severity of their abnormality. In the absence of any systematic judgments specific to this study, the coefficients were arbitrarily distributed at equal intervals on a zero to one scale. Mild, moderate and severely disabled children's lives were taken as 0.75, 0.50 and 0.25 of a normal life.

Table 1 Medical outcomes for 109 VLBW infants

Birthweight (g)	Infants	Survivors	Disabilities class			Number of QALs
			2	3	4	
500-599	2	0	0	0	0	0
600-699	5	2	0	0	0	2.00
700-799	9	1	0	0	1	0.25
800-899	12	6	1	0	0	5.75
900-999	9	3	0	0	1	2.25
1000-1099	17	11	1	0	1	10.00
1100-1199	16	10	0	1	0	9.50
1200-1299	10	10	1	0	2	8.25
1300-1399	20	18	0	0	2	16.50
1400-1499	9	8	0	0	0	8.00

It is possible to argue that the 0.25 coefficient attached to the severely abnormal category might be too high for some infants who could be placed close to the bottom of most scales, including the one used in the Canadian study which allows a negative value to be placed on some lives (Boyle et al, 1983). In a sample with a larger number of impaired infants, it would be important to establish a less arbitrary system for assessing the quality of life, but in this study the relationship between BW and outcome was shown to be insensitive to the selection of the quality adjustment coefficients. Results were also computed in terms of quality adjusted life years (QALYs) but are not presented since they do not differ substantially from those expressed in QALs.

Costs

Total costs in Table 2 were estimated as the sum of neonatal costs from birth to first discharge home, postnatal costs to the age of four years and projected life-time costs for abnormal children. They do not represent the full cost to society since, for instance, no attempt was made to measure private pecuniary and non-pecuniary costs to families. Nevertheless, the estimates capture a high proportion of exchequer costs.

Initial hospital costs included in-patient days in three Liverpool hospitals before or after treatment in the Regional NIC Unit. The cost of NIC was derived from an earlier study which was a full costing of the Unit. It involved the estimation of day costs for three levels of care: intensive, special and nursery. Each infant was costed individually according to the number of days spent in each care level. Surgery and diagnostic tests were costed separately.

Health service costs after the first discharge to home were made up of in-patient day and out-patient visits for each child up to the age of four. Work in progress will re-assess each child at the age of eight. It will identify and evaluate delays in educational development and subtler sorts of disability which may not have been evident at earlier ages. For the purposes of the present paper, it was assumed the VLBW children assessed as normal at age four, would not incur long-term medical costs above those of a child of normal BW.

An estimate was made of the life-time costs of care for disabled children from information provided by the Liverpool Education and Social Services Department. Moderately and severely abnormal children were assumed to require special nursery education when aged three and four, at a cost of £6,000 per child; special education from 5-15 years at £4,675 a year and from 16-18 years at £3,430 a year and institutional care from 19 to death, at £7,904 a year. Some of these disabled children and adults would receive part of their care at home

Table 2 Neonatal, postnatal and life-time costs of care for 109 VLBW infants – 1984 pay and prices. (Discounted at 5 per cent)

<i>Birthweight (g)</i>	<i>Total cost (£)</i>	<i>Average cost of a survivor (£)</i>	<i>Average cost of a QAL (£)</i>
500-599	1,188	–	–
600-699	33,000	16,500	16,500
700-799	146,012	146,012	584,048
800-899	140,267	23,378	24,394
900-999	114,187	38,062	50,750
1000-1099	235,836	21,440	23,584
1100-1199	210,472	21,047	22,155
1200-1299	276,746	27,675	33,545
1300-1399	275,011	15,278	16,667
1400-1499	61,890	7,736	7,736

but it was assumed that the cost to their families would be similar to the exchequer cost of institutional care. Mildly abnormal children were assumed to require no special care.

In Table 2 costs are expressed in 1984 pay and prices. Since these costs occur at different times, they are discounted at 5 per cent. Column 2, in Table 2, gives the cost per survivor. It is the total cost of caring for survivors and non-survivors divided by the number of survivors. Column 3 adjusts for the quality of life and gives the cost of producing a QAL. It is total cost divided by the number of QALs produced in each BW range.

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