

#### Nicholas D Embleton

Consultant Neonatal Paediatrician Royal Victoria Infirmary, Newcastle upon Tyne nicholas.embleton@ncl.ac.uk



Thomas Skeath Neonatal Research Fellow Royal Victoria Infirmary, Newcastle upon Tyne

## Does premature birth have implications for later adult health?

**C** urvival rates for preterm infants have increased dramatically over the last three decades. This is due to many factors: changing populations, better antenatal care including wide use of steroids, improved early respiratory management and nursing care, and better nutritional management. Despite this, impaired neurodevelopment and cognition in later life continue to be the major adverse sequelae of premature birth and this seems likely to remain a major issue for everyone involved in care of the newborn for decades to come. We are getting better but there is a long way to go and an awareness of more subtle cognitive or behavioural problems in adolescence or young adulthood, especially in the extremely preterm infant, is only emerging slowly.

But what of other outcomes; does prematurity have an impact on growth or blood pressure or type 2 diabetes in adulthood? Current data suggest early life events occurring *in utero* or during infancy may have profound effects on later metabolism, but most of this work is based on adults who were born at term. In recent years, however, concerns have been raised around whether growth promotion in premature infants may be helpful or harmful. While enhanced nutrition in the first few days and weeks seems to be associated with better cognitive outcome, there are concerns as to whether 'aggressive' nutritional practices may increase the risk of later metabolic harm<sup>1,2</sup>.

Animal studies ('cross fostering' rat studies) in the 1950s showed that nutrient deprivation in very early postnatal life permanently affected growth potential, whereas nutrient deprivation after weaning seemed not to result in permanent growth restriction<sup>3</sup>. This suggested that there might be critical windows in which nutrition permanently affects later outcome. Over the next three decades these ideas received little attention from mainstream medical researchers. The discipline, now amalgamated under the Developmental Origins of Health and Disease (DOHaD) label, did not receive widespread attention until the late 1980s when the work of Barker et al was published. David Barker, Professor of Epidemiology at Southampton, sadly died at the end of last year (August 2013) but his contribution to science was outstanding and the importance of his work continues to grow. The pioneering work of Barker's team showed consistent and large associations between birth weight and later risk of diabetes and cardiovascular health<sup>4,5</sup>. Initially, many in the

scientific community were sceptical but over the last two decades thousands of publications have confirmed the association between early life growth and later life chronic disease.

Barker's initial studies showed that infants born at term with lower birth weight had an increased adult risk of type 2 diabetes and cardiovascular disease. The interpretation of these findings is still the subject of much debate but the magnitude of the effects is large. The lifetime risk of chronic disease in an intrauterine growth restricted (IUGR) term infant weighing less than 2.5kg is similar to that of a normal birthweight infant, who as an adult then smoked 20 cigarettes a day. What might this mean for a premature infant, born weighing only 1.5kg?

Premature infants tend to grow poorly during their stay on the NICU or SCBU. This is a combination of many factors, in part because they are ill and have many morbidities, but also because we are just not very good at nourishing them. Parenteral nutrition (PN) is often started late and increased slowly, and the formulations of PN we have available are sub-optimal. Infants take time to tolerate milk feeds and despite the overwhelming advantages of expressed breast milk (EBM), most infants will need added fortifiers in order to meet nutrient requirements.

Premature infants are frequently discharged with weights less than the 10th centile and may therefore have a similar weight at 40 weeks corrected age (~2.5kg) to that of a term IUGR infant. Does this mean they will also have elevated risks for later metabolic disease? The short answer is maybe! Follow-up studies show that children and young adults who were born preterm have abnormal body composition (excess adipose tissue)6, higher rates of insulin resistance (which may lead to diabetes in later life) and higher blood pressure. These risks seem highest in the most prematurely born individuals. However, the data do not currently suggest that this is primarily due to nutrition over the first few weeks and months. There seems to be something fundamentally different in how their metabolism is 'programmed' that may explain why these effects emerge in later life.

Early life nutrition may affect later growth and disease through a variety of mechanisms including permanent structural change, accelerated cellular ageing, changes to endocrine systems and programming effects<sup>7</sup>. There are several molecular processes involved, many of which appear to involve what is termed epigenetics – changes to

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the way our DNA functions, ie how and when our genes are transcribed to produce proteins<sup>8,9</sup>. In epigenetics, the basic sequence of DNA that makes up our chromosomes is not affected, but instead external modifications (eg the adding of methyl groups) result in genes being switched on or off and may be one of the mechanisms by which early life events programme later outcomes.

What does this mean for those of us who work in the NICU or SCBU? The two most important lessons remain:

- 1. Except in very rare situations, breast milk is always better for an infant than formula milk
- 2. Failure to meet nutrient requirements in

early life is likely to result in permanent cognitive disadvantage.

Now we are faced with the prospect that how we feed infants and how they grow is likely to affect how healthy they are for the rest of their lives. Neonatal nutrition matters now and when you are in your 70s!

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