EARNEST – Cambridge, December 2006 – Background paper

Extracts from Dr Mary Fewtrell's presentation at the EARNEST Symposium at the Nutrition Society meeting 13th December 2006

EARNEST - the Early Nutrition Programming Project

EARly Nutrition programming - long term Efficacy and Safety Trials and integrated epidemiological, genetic, animal and consumer research.

Increasing evidence from lifetime experimental studies in animals and observational and experimental studies in humans, suggests that pre- and post-natal nutrition ***programme*** long-term health. However, key unanswered questions remain on the extent of early life programming in contemporary European populations, relevant nutritional exposures, critical time periods, mechanisms, and effectiveness of interventions to ***prevent or reverse programming effects.***

The EARNEST Research Consortium brings together a multi-disciplinary team of scientists from European research institutions in an integrated programme of work including experimental studies in humans, modern prospective observational studies; and mechanistic animal work including physiological studies, cell culture models and molecular techniques.

Theme 1 tests early nutritional programming of disease in humans, measuring diseases markers in childhood/early adulthood in 19 randomised controlled trials of nutritional interventions in pregnancy/infancy.
Theme 2 examines associations between early nutrition and later outcomes in large, modern, European population-based prospective studies, with detailed measures of diet in pregnancy/early life.
Theme 3 uses animal, cellular and molecular techniques to study lifetime effects of early nutrition.
Biomedical studies are complemented by studies of the social and economic importance of programming in **Themes 4 and 5**, and packages encouraging integration, communication, training and wealth creation.

The EARNEST project aims to:

- help formulate policies on composition and testing of infant foods to improve the nutritional value of infant formulas
- identify interventions to prevent and reverse adverse early nutritional programming.

In addition, EARNEST has the potential to:

- develop new products through industrial partnerships
- generate information on the social and economic cost of programming in Europe
- and help maintain Europe's lead in this critical area of research.

There is increasing evidence that health and development in adult life are influenced or 'programmed' by factors operating during fetal life and infancy. Whilst the general concept of programming has been recognized for several centuries, evidence that nutrition could operate as a programming stimulus or insult is more recent.

The pioneering work of ***McCance and Widdowson*** in the 1960s demonstrated in animals that *nutrition* could act during critical windows early in life to affect long-term outcomes. For example, they showed that rats raised in small litters, and therefore overfed early in postnatal life, developed greater body size as adults. There is now overwhelming evidence that early nutrition in a variety of animal species, including primates, can influence later cardiovascular disease, including all components of the metabolic syndrome, learning and behaviour, intermediary metabolism, gut function, bone health, immunity and longevity.

Evidence of nutritional programming in humans has, until recently, come largely from historical observational studies, that have shown associations between small size in early life and adult disease risk. These cohorts have been constructed from available maternal or child health records and have necessarily relied on indirect measures of maternal and infant nutrition (rather than direct measures of maternal or infant diet) and lacked detailed data on potential confounding variables. Many of these cohorts were born before the Second World War and it is possible that the nature and size of the associations is different in contemporary European populations. While these studies have generated considerable interest they have been unable to examine the association with diet directly or establish whether associations are causal. Hence they cannot be used to underpin infant feeding recommendations.

More recently, evidence for nutritional programming has been obtained in experimental studies in humans. These studies have demonstrated a causal relationship between nutrition in infancy and later outcomes, including cognitive function and cardiovascular risk factors. Moreover, the data suggest that the effect size for the influence of early nutrition on later health outcomes is likely to be large. For example, the reported effect of early growth and nutrition on later diastolic blood pressure (around 3-4mm effect size) is greater than all other non-pharmacological means of reducing blood pressure such as weight loss, salt restriction, or exercise.

These data must be viewed against the finding that lowering population-wide diastolic blood pressure by only 2 mm Hg would be expected to reduce the prevalence of hypertension by 17%, the risk of coronary heart disease by 6% and the risk of stroke/transient ischaemic attacks by 15% and prevent 100,000 vascular events annually among those aged 35-64, in the USA alone.

Despite rapid progress in the field of programming research over the past decade, several key questions remain:

- What is the extent of early life programming in contemporary populations?
- What are the relevant nutritional exposures?
- What are the critical time periods?
- What are the underlying mechanisms?
- What are effective interventions for preventing or reducing adverse programming effects?

The Early Nutrition programming Project aims to address these issues, using an integrated approach that brings together work from **robust experimental studies in humans** backed by **modern prospective observational studies**; and **mechanistic animal work** including physiological studies, cell culture models and molecular techniques.

Benefits for an integrated approach to Nutritional programming research
Evidence for nutritional programming has come from three types of study - animal studies, human epidemiological studies and human experimental studies. Each approach has its advantages and disadvantages:

Randomised controlled trials (RCTs) in humans are regarded as methodologically the best approach for underpinning health policy. They equalise unknown as well as known confounders and so can establish causation; they permit quantification of the effect size and so can be used to estimate economic benefits; and they can detect and quantify adverse effects and thus address safety aspects. Nevertheless, in the context of nutritional programming of disease later in life, they have certain limitations. Many of the disease outcomes will not become apparent for decades, necessitating the use of 'proxies' of later disease risk that can be measured at younger ages.
Historical cohort studies have the advantage of generating rapid results, and often allow investigation of early life factors and disease end-points (for example, occurence of or death from ischaemic heart disease). However, the quality of data from pregnancy, infancy and childhood - in particular nutritional exposures - may be sub-optimal since the cohorts were not designed for this purpose. Furthermore, since many of these cohorts are from previous generations, the generalisability of the results to modern populations may be questioned.
Modern **prospective observational studies** identify defined (generally large) populations, measure them precisely and follow them up longitudinally. They therefore have better measures of exposure and confounders than historical cohort studies. Of great relevance to the type of project we envisage, prospective cohort studies may embody very detailed early data including physiological, biological and social information on the subjects and are thus able to control for known confounding factors. Moreover, more recent prospective studies (e.g. ALSPAC) have contemporary relevance and are not investigating practices and environmental conditions relevant 60-80 years ago. However, these modern cohorts share some of the limitations of intervention trials in terms of the need to use proxies for later disease risk.
Animal studies allow rapid study of the life-time consequences of interventions, with a greater variety of nutritional interventions than may be possible in humans, and easier collection of tissue and organ samples. They therefore enable greater investigation of underlying mechanisms of nutritional programming, and better identification of the precise developmental windows in which global or specific nutritional imbalances contribute to later disease. Relevance of the findings to humans may be questioned.

It is clear from these considerations that there are considerable benefits from adopting an approach that combines the strengths of these different types of study. The ENPP therefore aims to

1) test early nutritional programming of adult disease risk in humans by measuring disease markers in early adulthood in **well-conducted randomised controlled trials** of specific nutrition interventions in pregnancy and infancy.
2) estimate the importance of nutritional programming in contemporary European populations by examining the associations between early nutrition and later outcome in **large well-characterised population-based prospective studies** with detailed measures of diet in pregnancy and the first years of life.
3) these observational studies will allow identification of dietary exposures that can be explored in animal models and eventually tested in future trials in humans; study

mechanism; and confirm whether findings from laboratory studies translate into diet-risk associations in free living humans.

4) use **animal, cellular and molecular techniques** to study lifetime effects of early nutrition. These studies will seek to refine models of nutritional programming in order to identify *mechanisms and critical periods* in development, where the foetus or infant is most susceptible to nutritional influences. These studies will inform the analyses conducted in the observational studies and help prioritise future trials in humans.
5) use developments in **functional genomic techniques** to further explore the basis of early nutritional in programming in clinically relevant model systems and in the prospective cohort studies (all of which have collected and stored biological samples)

The ENPP consortium consists of a multi-disciplinary team of 40 partners (33 academic institutions, 3 industry, 4 SME) in 17 EU countries with a coordinating centre in Munich. The project commenced in April 2005 and runs for 5 years.

Scientific Integration

A key aim is to integrate as far as possible the different components, relevant at a number of levels - both between and within themes. For example, the exchange of results between partners involved in animal and human studies is important in order to maximize the use of findings in the design and analysis of ongoing studies. Integration is also important between and within Themes 1 and 2. For example, within Theme 1, the protocols and follow-up data of the studies conducted to date are being compared to identify common interventions and outcomes which might usefully be combined for the purpose of meta-analysis. Secondly, many of the proposed follow-ups to be conducted within Themes 1 and 2 involve the same outcome measures. The identification and standardisation of these outcome measures across different studies at an early stage will facilitate pooling of data and meta-analyses, providing the statistical power necessary to detect meaningful effects of early nutrition on a number of aspects of long-term health.

This approach has already been adopted successfully in Theme 1, in the design of the protocols for follow-up of LCPUFA-supplementation trials, which are being conducted by our own centre in London and the University of Groningen in the Netherlands. One of the problems identified in this field is the inconsistency of outcome measures, making comparisons between published studies almost impossible. For this reason, the two groups involved in LCPUFA follow-up trials within the ENPP have identified and agreed on a common battery of detailed cognitive and neurological tests to be used in all subjects at follow-up, which will make future comparison of findings easier. Training in these techniques was then made available to all partners at a workshop organised as part of the designated Training Theme. A similar strategy has been adopted for other outcome measures such as anthropometry, measurement of body composition (at a number of levels of complexity) and blood pressure.

Thus, whilst each activity is individually of high quality, the value of the integrated project is expected to exceed that of the individual parts. Data of this nature are not available elsewhere and will have considerable importance for health policy in Europe, but also worldwide. DNA banks will also have been established, offering a valuable resource for test ting new genetic hypotheses in the future.