Summary

Marabou Conference 2005: Nutrition and Human Development

The 2005 Marabou Conference highlighted the re-emergence of nutritional issues as not only scientifically very exciting and fundamentally involved in the most fascinating areas of current molecular biology and the interpretation of functional genomics, but also now of special interest to those involved in explaining possible differences in ethnic sensitivities to the principal disease burdens of our time.

THE NUTRITIONAL DEBATE A CENTURY AGO

Very few scientists working in the control and modulation of development realize that many of these same issues confronted leading thinkers a century ago, when there seemed to be remarkable differences in the size, well-being, and ability of children within a single country. For example, it was recognized that there had been a deterioration in the heights of the working class in the United Kingdom over many decades as families were drawn from their agricultural environment into the rapidly changing, industrializing towns and cities. Previously, the men had been tall and strong, ideal recruits for the army, but they had now become too puny to pass even the recruitment tests. This began the nature versus nurture debate, which was only resolved when new findings about the significance of animal protein for promoting children’s growth and the discovery that trace amounts of substances in food called vitamins were backed by trials of the differential effect of food supplements on stunted children.

These experimental studies fueled the campaigns to improve the availability of nutrient-rich foods to provide adequate amounts of energy and protein to allow normal infant and childhood growth with appropriate development in even the poorest children. Poverty had clearly been linked to very limited, poor-quality diets, but little was done until the United Kingdom established what was in effect a mass national experiment of food rationing for the whole population during the Second World War. Based on these novel scientific principles, every child and adult’s ration was set on sound quantitative principles of nutritional need, with vulnerable pregnant women and lactating mothers and their children being given special supplements of orange juice, milk, and cod-liver oil to boost their intakes of what were then considered to be their special requirements for animal protein, calcium, and vitamins C, B2, A, and D. This gamble was precipitated by the recognition that the war could well be lost at sea because of inadequate food imports rather than on the battlefields of Europe.

THE TRANSFORMATION OF THE FOOD CHAIN AND DISEASE PATTERNS FROM THE 1940s ONWARDS

The success of these wartime policies, with overall death rates falling and children growing well, led to a complete change in the thinking of governments throughout the world. Nobel Prize-winning scientists had provided crucial new knowledge, which in practice had saved the Western world. This meant that adequate and appropriate food provision was not only an issue relating to a poor family’s competence to earn a living, but had become a question of national security. Thus, it was important to develop the concept of a cheap food policy to allow all workers and their families to be effective citizens—a major boost in national agricultural production was therefore linked to concepts of national security and economic development. The control of food supplies therefore became a strategic national interest, so the promotion of intensive agriculture and the development of a food industry to ease the provision of food for working mothers was clearly beneficial. There followed a remarkable increase in national food production, with the intense promotion of meat, milk, butter, and sugar production and consumption.

Unfortunately, the practical application of these nutritional and public health policies transformed the disease patterns of the Western world with a rapidly rising incidence of coronary artery disease and some cancers. The cardiovascular findings led to a slow change in public health policies on fat sources, but as cardiovascular deaths decreased in the developed world, type 2 diabetes progressively increased, with obesity becoming recognized as a major problem only in the last decade. Now the lower- and middle-income countries are being nutritionally transformed with a seemingly even more rapid increase in heart disease and diabetes. Obesity,
especially abdominal obesity, seems to induce far greater health problems with only modest weight gains in the lower- and middle-income countries of the developing world as they import Western diets and cultural habits. The remarkable escalation of diabetes and cardiovascular disease, particularly in populations currently and previously subjected to malnutrition, now reveals unusual susceptibility that seems to be related to the conjunction of fetal malnutrition and later inappropriate diets. The molecular, cellular, and nutritional basis for these linkages was the theme of this conference.

FETAL PROGRAMMING AND EPIGENETICS

The standard explanation for ethnic differences has been that as man evolved and migrated out of Africa, genetic selection in different environments led to markedly different disease patterns in different societies. Thus, the Indians’ extraordinary susceptibility to type 2 diabetes was presumed to relate in some way to extreme selective pressures. Yet David Barker with others had highlighted the association between babies born small, presumably because of disadvantageous fetal conditions and these individuals’ subsequent susceptibility to abdominal obesity, diabetes, and hypertension. Furthermore, a host of experimental evidence in pigs, rodents, and primates had shown decades ago that nutritionally limited diets during pregnancy postnatally altered permanently not only the size of the adult animal but also their organ sizes, proportions, organ structure, metabolic capacity, and responsiveness as adults to nutritional input and other stresses. This implied that altered nutrition during the course of development could permanently affect the metabolic responsiveness of offspring. The question then was, what mechanisms could be responsible for this array of effects, which implied that one could in some way “program” a body’s responsiveness and its apparent intrinsic capacity to cope within a single generation rather than over a period of centuries of progressive genetic selection?

Wolf Reich described what are now called “epigenetic mechanisms,” which are fundamental to the processing of the fertilized ovum, and select from the combination of the inherited paternal and maternal genes those determining not only the sex of the child but also those genes that control the development of the placenta, fetal and postnatal growth, and the development of the child. There is an intrinsic competition between the paternal and maternal genes for early growth, with the maternal genes having to dominate to ensure that the fetus is of an appropriate size for the mother’s uterus and capacity to provide nutrients.

The selective differential regulation of the different genes is accomplished by marked methylation of both the DNA relating to the promoter regions of genes and to methylation and acetylation of the histones covering the DNA, therefore allowing selective access to particular DNA sites for the methylation process. This methylation suppresses the expression of the gene and thereby alters not only the expression of genes determining the structure and array of enzymes within the cell, but also the reactivity of these genes to metabolites. In many cases, one allele is silent in most tissues throughout development. The alleles still have a memory of their parental origin and as the fetal cells divide, these genes are replicated and preserved through subsequent cell divisions. The genomic imprinting by methylation can then not only affect the individual then developing but also the fetal gonads. Thus, a single insult to which a mother is exposed can not only affect her children but also her grandchildren, if not further generations. Methylation and demethylation processes may affect the genetic responsiveness at very different times of life, with about 80 genes already identified as subject to imprinting, which can also involve the small inhibitory RNAs. In another mechanism, the ability of shared activating sequences (enhancers) to activate an imprinted gene is determined by a chromatin boundary element present on the unmethylated allele between the two genes. Thus, there is a very complicated array of mechanisms that can determine during development the temporary or permanent expression of particular genes.

CRITICAL PERIODS AND THE DEVELOPMENTAL PROCESS

The control of the developmental process begins immediately at conception, with increasing evidence that the blastocyst is vulnerable to the impact of different nutrient concentrations in the oviduct fluid, such as the level of nonessential amino acids and the vitamins and metabolites involved in promoting the turnover of the one-carbon pool necessary for DNA replication. The essential fatty acids may also modulate the developing responsiveness of cells, as well as the process of placentation and its control, which is also affected by a substantial number of different genes. Increasing evidence suggests that the growth trajectory of the fetus is determined very early after conception, with the evolving placenta not simply providing a mechanism for nutrient transfer but also operating as a signaling system to ensure that appropriate amounts of maternal nutrients are supplied to fit the newly established growth trajectory of the fetus.

Humans may be unique relative to other mammalian species in their high rates of gestational fetal loss, these high rates perhaps reflecting a unique selective pressure that accelerates the expansion of polymorphic alleles
within human populations. Approximately half of human embryos fail to implant, but no molecular mechanisms controlling this survival have yet been demonstrated. However, the variant alleles of methylenetetrahydrofolate reductase and transcobalamin impair the metabolism of folic acid and homocysteine and are independent risk factors for inducing fetal losses.

The implantation process is under many gene influences, with some genes controlling the overall growth of the placenta and others affecting the thickness of the barrier to nutrient exchange and the control of nutrient transporter expression. The insulin growth factor 2 gene is a product of parental genes that tend to promote fetal growth by promoting good nutrient exchange by the placenta. Thus, although the fetus is obviously dependent on its mother’s nutrient supply, it also influences its own development by altering the demand for nutrients. This may be mediated by alterations in fetal and maternal blood flow by the placental production of angiogenic factors that promote vasodilatation. The placenta also produces metabolic hormones such as placent al lactogens and placental growth hormone, which alter insulin production and promote insulin resistance in maternal tissues to increase glucose availability to the fetus. The placenta also produces maternally circulating leptin and ghrelin, as well as accumulating glycogen in times of glucose plenty; fetal genes also determine changes in placental nutrient transporters. Placental development is highly adaptable, and many types of compensation are possible in response to suboptimal nutrition of the mother.

Despite this adaptive capacity, however, there is now increasing evidence that there are multiple stages in the developmental process whereby the early growth trajectory of the fetus and its subsequent development is geared to strong maternal influences, which in evolutionary terms is conditioning the fetus for its future extra-uterine life on the basis of the mother’s own nutritional experience. Thus, many of the public health problems that we may now be seeing reflect an intergenerational disjunction as the offspring are confronted by a completely different environment to which the child-imprinted genes provide limited adaptive capacity. The challenge is to discriminate the crucial role of nutrient and other maternal needs at each stage of pregnancy (and indeed of ovum development), which affects this adaptive capacity.

**KEY NUTRITIONAL FACTORS IN PREGNANCY**

Nutrition in pregnancy has been recognized for millennia as important, but we still do not know what the real nutrient needs of the pregnant women are. Alan Jackson now highlights new evidence suggesting that the length of the baby at birth and in infancy is related to the availability of the nonessential rather than the essential amino acids. In pregnancy, this is related to the levels of protein turnover of the mother, which in turn is related to her height as a crude index of her lean body mass. The protein and energy intake of the mother is important when she is on marginal diets, but too is her long-term intake of the essential fatty acids—particularly the n-3 long-chain fatty acids, which are not only required for the formation of the cellular membranes during growth, but also for appropriate cellular reactivity. Furthermore, there is now clear evidence of the essentiality of adequate fetal and postnatal amounts of these n-3 fatty acids for normal visual and brain development.

The importance of the vitamins for appropriate fetal development has also been accepted for many years, with clear evidence that folic acid supplements will reduce the incidence of fetal neural tube defects if provided early enough in pregnancy. Given the importance of folate for nucleic acid synthesis and for a host of methylation processes, the importance of an adequate supply of the array of nutrients needed for these processes (e.g., folate, riboflavin, pyridoxine, and vitamin B₁₂) is biologically understandable but not always clearly documented by controlled trials. New evidence from Yajnik in India, however, suggests that vitamin B₁₂ deficiency is highly prevalent there, and is a potentially crucial mechanism in this predominantly vegetarian society for explaining the limited lean tissue growth of so many small but fat Indian babies with their programmed susceptibility to disease.

Nutritional adequacy relates not only to amino acids, essential fatty acids, and vitamin supply, but also to mineral nutritional adequacy. The crucial role of iodine both in pregnancy and throughout life is well known, but adequate iron is also crucial at critical stages in brain development.

It is also becoming clear that our focus should not be simply confined to nutrition if we are to be concerned for the appropriate development of the child. The nature of maternal care may also depend on the visual, tactile, and other processes involved in breast-feeding, which may involve further imprinting by methylation processes of both maternal and child behavior. There is clear evidence that the long-term mental capacity of the child is affected by the mother’s interaction with the child. There is also experimental evidence that nutrient-glucocorticoid regulation of behavior such as violence and stress, as well as the propensity to abdominal obesity and metabolic changes with increased susceptibility to type 2 diabetes, can be conditioned by complex methylation and demethylation control of promoter regions of glucocorticoid
receptor systems in different parts of the brains as the cerebral structures develop.

NEW GROWTH STANDARDS AND THEIR IMPLICATIONS

The new evidence on the importance of prolonged breast-feeding for ensuring both adequate and appropriate growth of the infant is about to be highlighted by the development of the first growth standard curves for 0- to 5-year-old children born of adequate weight to suitably selected non-smoking affluent women in Brazil, the United States, Norway, Ghana, Oman, and India. The mothers were also provided with recurrent and often intensive advice on appropriate feeding, immunization, and other optimum rearing practices. These growth curves will therefore no longer be considered as charts for reference to provide easy national comparisons. Instead they provide for the first time a set of standard or “ideal” curves, since they show a remarkably similar growth patterns and surprisingly little variation despite the different environmental and presumably different genetic background and epigenetic conditioning of the mothers. These children grow in a surprisingly uniform manner.

These optimum growth curves do not, however, tell us about the longer-term impact of the child’s inherited complement of genes with their epigenetic changes. We already know that the length of the child and his or her eventual stature is very different in different societies, with further evidence that northern Europeans are continuing to grow surprisingly tall. Thus, the interaction of paternal and maternal genes affects an individual child’s response to their postnatal diet and infection-free environment, but further evidence is emerging on what seems to be a special height-promoting effect of high milk intakes.

THE NUTRITIONAL TRANSITION: A NEW SCIENTIFIC AND PUBLIC HEALTH CHALLENGE

In most societies, this increase in final height is being accompanied by the amazingly rapid emergence of childhood obesity, a feature that has never been seen before. Now young women are increasingly entering pregnancy when overweight as the dietary habits of girls and young women appear to be deteriorating in many societies throughout the world. The increasing overweight is accompanied by a marked increase in gestational diabetes together with an unprecedented rise in the prevalence of large babies. This is accompanied by increasing risks of fetal malformations, damage to mother and child during parturition, and an increased risk of both obesity and type 2 diabetes in the adolescent child and the mother.

We therefore seem to be in the middle of a rapid nutritional transition affecting the majority of the world. The combination of the epigenetic conditioning of many generations to a nutritionally inadequate, unsanitary, and infection-laden environment is now in the current generation being confronted by a totally new world of effective immunization, improved sanitation, and mechanization, with limited demands on physical activity and an intense promotion, even to children, of what we now recognize are very inappropriate high-density, nutrient-poor foods.

The alarming escalating health problems, with two-thirds of the world’s population seemingly supersensitive to excess weight gain, diabetes, cardiovascular disease, and perhaps to many cancers, present new public health challenges. These will be amplified by the intergenerational amplification of the emerging obesity and diabetes epidemics. Therefore, despite our poor understanding of the extent and reversibility of the epigenetic and other nutrient-related changes in organ and metabolic programming, we are now confronted with demands for judicious action to protect not only the current generation of children, but also the well-being, mental, and economic capacity of future generations.

Current policies are being threatened by a crude approach to public health that does not yet recognize the importance of ensuring that global trade and the promotion of nutritionally inappropriate diets in a vulnerable world need to be altered to cope with the fact that we are dealing with global populations in need of coherent new nutritional policies. There are now far more genetically related constraints and opportunities for conditioning the well-being of future generations than we ever imagined. Once again, as occurred a century ago, we need more groundbreaking basic science and for scientific analyses to be linked to issues of immense societal concern so that geneticists, biologists, doctors, and governments can all contribute to the future well-being of vulnerable populations.