

## Early Influences in Childhood Obesity—Implications for Adult Metabolic Disease

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In the past 20 years, an epidemic of adult and childhood obesity has swept through the developed world resulting in the “globesity” epidemic. This is clinically significant since obesity is a major risk factor for many chronic diseases which now occur earlier in life. Recent landmark research has identified that the intrauterine and early postnatal environment can strongly influence the risk of developing obesity and other problems in later life. The 9 months of gestation constitute the most critical period of life when the embryo miraculously develops and early life influences encountered in-utero will shape the fetus’ susceptibility to disease and its metabolism. These prenatal influences include the nutrition, drugs, chemicals and infections which the fetus was exposed to in the womb, which can significantly influence fetal development.

The pioneer of the fetal origins concept was David Barker who postulated that poor nutrition during critical periods of development can influence adult susceptibility to cardiovascular disease, type 2 diabetes mellitus and obesity.<sup>1-3</sup> The mechanism for this lies in fetal programming, which refers to the physiological adaptations leading to life-long changes in structure and function of the body. It is as though the baby receives a forecast of the nutritional environment it will encounter after birth and adapts its physiology and metabolism accordingly. This adaptation is detrimental if there is a mismatch between the predicted and actual postnatal environment.

Although the environment has been considered to be the main contributor to the obesity epidemic, the missing link between genetics and the environment is likely to found in the field of epigenetics, which has revolutionised modern biology. Epigenetics describes how the environment influences the phenotype through changes in gene expression by the addition of chemical groups to DNA which do not change the genetic code, but will change the expression of nearby genes.

Many studies on rodents have demonstrated that prenatal and postnatal environments can influence the risk of

future obesity. When rats are fed with a protein-restricted diet from conception throughout pregnancy, the offspring develop obesity with hypertension, glucose resistance and dyslipidaemia.<sup>4</sup> Female rats fed an obesogenic high-fat diet before mating and peri-conceptually gave birth to obese offspring with higher blood pressure and insulin resistance compared to control offspring.<sup>5</sup> In the rat model, reducing the mother’s food intake at conception and pregnancy at critical periods of development also led to persistent changes in gene expression, adversely affecting carbohydrate and lipid metabolism.<sup>6,7</sup>

Early nutrition can influence DNA methylation through diet methyl donors such as choline and methionine. Rats fed a folate-deficient diet exhibited a change from normal DNA methylation to global DNA hypomethylation. Folate supplementation restored DNA methylation, which was the basis of this landmark experiment on the yellow agouti mouse.<sup>8</sup> The agouti gene results in a yellow pigment, rather than the brown pigment. Maternal dietary methyl supplementation with folic acid, vitamin B12 and choline increased methylation at the agouti gene promoter and shifted the coat color distribution of the offspring towards the brown color. Interestingly, the yellow mice were more obese, more insulin resistant and developed diabetes mellitus. This is epigenetics in play as reducing methylation of the agouti gene led to obesity and insulin resistance.

The role of epigenetics in the development of human obesity is now an area of intense research, as it may provide pivotal clues to the fetal origins of obesity and the metabolic syndrome. Insights into this concept are offered through 2 historical periods of severe famine which provide a unique opportunity to study the effects of extreme dietary restriction on the population.

### The Dutch Hunger Winter

The Dutch Hunger Winter lasted from November 1944 to late spring 1945 and was a bitterly cold period in Western Europe, creating extreme hardship.<sup>9</sup> However, this was a

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perfectly designed but tragic experiment in nature. There were previously well-nourished women who suffered just one period of malnutrition at the same time allowing us to examine the effects of intrauterine deprivation on adult health. The study established that women exposed to famine from mid to late gestation had babies with significantly reduced birth weight. Compared to controls born before or conceived after the famine, people exposed to famine in early gestation had a more atherogenic profile, higher body mass index (BMI) and a higher risk of coronary heart disease. Those who were exposed to famine in mid or late gestation had reduced glucose tolerance with increased insulin resistance.

Heijmans et al<sup>10</sup> subsequently discovered hypomethylation of the maternally imprinted *IGF-2* gene in individuals who were prenatally exposed to the Dutch Hunger Winter famine. Methylation of *IGF-2* silences gene expression while demethylation enables gene expression. The phenotypic consequences of hypomethylation have been implicated in the metabolic syndrome. Even more interestingly, Heijmans found that 6 decades after the famine, there was persistent hypomethylation of *IGF-2* gene in those prenatally exposed to famine as compared to unexposed same-sex siblings. Since *IGF-2* is a key factor in human growth and development, demethylation of *IGF-2* suggests that early life environmental conditions which cause epigenetic changes in humans, persist throughout life!

### The Chinese famine

“The 3 years of Great Chinese Famine” from 1959 to 1961 were caused by abnormal severe drought, flooding and unwise policies of the Communist Party of China. There were an estimated 43 million famine victims. This famine lasted longer and affected more people than the Dutch Hunger winter. Li et al<sup>11</sup> established that adults who were exposed to famine during fetal life had a higher risk of metabolic syndrome as compared with non-exposed subjects, odds ratio 3.13 (95% CI, 1.24 to 7.89,  $P = 0.016$ ). For adults exposed to famine during early childhood the odds ratio for metabolic disease was 2.85 (95% CI, 1.19 to 6.83,  $P = 0.019$ ).

There seems to be converging data to support the hypothesis that individuals who suffered from inadequate nutrition and metabolic disturbances during fetal and postnatal development underwent incorrect ‘epigenetic programming’ and developed the metabolic syndrome. At present, there is strong evidence that environmental changes can result in the metabolic syndrome through the epidemiological studies of Barker and the famine studies which all demonstrate that early nutrition is associated with subsequent metabolic problems. From the extended Dutch Hunger Winter study, there is also evidence that

environmental changes can cause hypomethylation of the *IGF-2* gene locus. However, there is no evidence to demonstrate that these epigenetic changes directly cause the metabolic syndrome. Nonetheless, the agouti mouse model clearly demonstrates epigenetics through environment-induced gene expression causing obesity and the metabolic syndrome. Perhaps, this hypothesis may prove to be true for humans.

Deciphering the epigenetic targets and mechanisms of dysregulation by environmental exposure is the first step to translation into clinical practice. Altered epigenetic patterns may serve as biomarkers for predicting disease. They may provide new opportunities to develop prophylactic dietary strategies, akin to the use of folate for pregnant women which has reduced the spina bifida incidence. There is also the potential for the development of new drugs which can modify epigenetic changes in the form of DNA methyltransferase inhibitors and histone deacetylase inhibitors.

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