



## The Predictive Adaptive Response in relation to Epigenetics and the concepts of 'Thrifty Genotype' and 'Thrifty Phenotype'

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### INTRODUCTION

In 1968, Conrad Waddington (1905 - 1975) first coined the phrase "epigenetics" which means "In addition to genetics". It is the study of changes in genetic expression that are not linked to changes in the DeoxyriboNucleic Acid (DNA) sequences, but are related to the influence of the environment on the genes being expressed or not. In essence, certain genes carry a sign that says "Ignore me" and these genes are silenced. Other genes carry a sign that says "Pay attention to me" and these genes are activated. It has been found that not only are the genes themselves inheritable, but also the patterns of these signs are too. i.e. "Pay attention to me", "Ignore me", "Pay attention to me", "Ignore me" etc. Epigenetics has added an entirely new dimension on inheritance which extends way beyond DNA. Studies have found that a control system of switches exists that either activate or silence genes in response to life experiences including: the environment, nutrition and stress to name but a few. These factors can exert tremendous control on these switches with their actions being passed on as part of a non-DNA form of inheritance.

### Genotype and Phenotype

Your genotype is defined as your specific genetic makeup, your particular genome, in the form of your DNA. Your phenotype is your total physical appearance and constitution. Therefore it is thought that:-

$$\text{Genotype} + \text{Environment} = \text{Phenotype}$$

Using an analogy from the construction industry:-

- **Genotype** would be the set of drawings produced by an architect when designing a house
- **Environment** would be the skills of the construction workers and/or the quality of the building materials used
- **Phenotype** would be the finished house

Once a mother's egg has been fertilised by a father's sperm, it is subjected to profound and life changing events, which are heavily influenced by it's environment, which in this case is the mother. The original single strand of unique DNA (genotype) is used as a template and by the addition of it's environment it's phenotype begins to develop as the physical manifestation of who it will become.

### PREDICTIVE ADAPTIVE RESPONSE (PAR)

In 2005 Peter Bruckman and Mark Hanson published a book entitled "*The Fetal Matrix*" followed by further work in 2008 and 2010 called "*Predictive adaptive responses in perspective*" and "*Predictive adaptive responses and human evolution*". Their work advanced observed effects of starvation in post war survivors of a historical incident in Holland in the winter of 1944-45 called "The Dutch Hunger Winter" and changes that were produced in laboratory experiments in a golden furred mouse by altering the diet of its mother.

### The Hunger Winter ('Hongerwinter' in Dutch) – Holland 1944-45

Field Marshall Montgomery's second world war operation named "Operation Market Garden" which became known as "A Bridge too far" met strong resistance at a bridge in Arnhem, which caused major consequences for the people of the area and their offspring due to it's failure. Due to a serious of disastrous events, the

Nazis blew up all of the dykes and dams in western Holland and with all railway tracks, ferries and parts of the highways sabotaged, the Dutch were held hostage with no possibility of any food supply.

The Dutch underground transmitted radio messages which reached London on September 27, 1944. They warned that there was only enough food left for a few weeks. There followed one of the coldest winters in European history and things just got worse for the stranded people in western Holland. The local harvest was not big enough to supply the large cities and people were forced to walk for hundreds of kilometres to trade their valuables for food. They were forced to consume sugar beet and tulip bulbs just to survive. By early 1945, official rations were 400-800 calories per day and approximately 30,000 Dutch people had starved to death.

However, during this terrible time for the people of western Holland, some 40,000 babies were born and their name, birth date and weight were recorded. By the 1960's when these famine survivors had matured into fully-grown adults, researchers studied them and found some truly alarming and shocking results. All of them had the usual medical complications, but attention was drawn to the fetuses who were in their last trimester during the height of the famine. All of them had very low birth weights. They grew up normally but then suffered from very high rates of diabetes in later life. On the other hand, they found that babies who were in the first six months of gestation during the height of the famine, were of a normal birth weight, but gave birth to unusually small babies in adulthood.

The foetuses that had been exposed to famine during gestation also went on to develop more obstructive pulmonary and kidney disease. Those whose mother's starved at the beginning of their pregnancies had more atherosclerosis, altered blood clotting, more obesity and a three-fold increase in cardiovascular disease. They also found that women were affected differently to men. Offspring of mothers pregnant during the famine suffered as follows:-

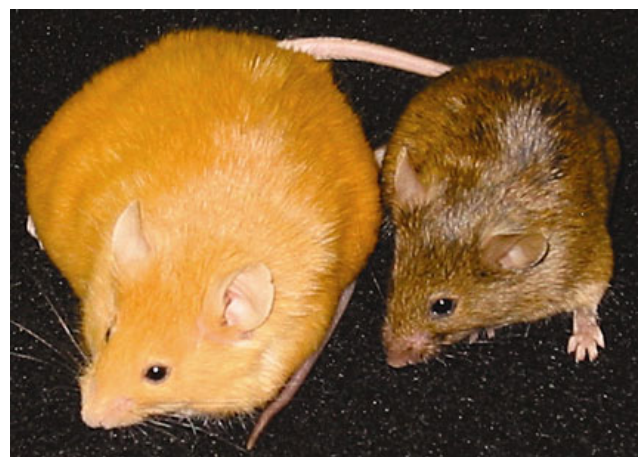
- **Daughters** were significantly more diabetic and obese ("diabesity") at midlife than average.
- **Sons** had significantly higher rates of schizophrenia and an exaggerated response to stress.

So evidence suggests that the dreadful consequences of the Dutch "Hungerwinter" led to dramatic health effects being inherited by their offspring decades after the famine. It appears that you are not what you eat, but more likely what your grandmother did not!

### The Agouti Mouse Experiment

Early in the new millennium a fascinating medical study was performed on a chubby golden yellow strain of mice named "agouti mice". They are named after a variant of gene that they possess which in normal circumstances gives them yellow fur. It was found that if the agouti gene is silenced by having methyl groups attached to it, then the agouti turns the colour of the fur a brownish colour. In addition to the yellow fur, the mice were bred to develop both diabetes and obesity in early life.

The first study was published in 2003 in which pregnant agouti mice were fed lab chow mixed with methyl rich supplements such as vitamin B12, betaine hydrochloride and folic acid. The control group however were just fed lab-chow. The offspring of the mice who had received the supplements were visibly different to the ones who



**Above:** With no more than a change in diet, laboratory agouti mice (left) were prompted to give birth to young (right) that differed markedly in appearance and disease susceptibility<sup>(1)</sup>.

hadn't. They had mostly brown fur whereas the control mouse had yellow. They were very lean whereas the control mice were susceptible to obesity, diabetes and cancer. Most fascinating was the fact that the methylated, lean, brown mice maintained their state throughout their lives. So supplementing with methyl groups had modified the agouti gene, not just in the mother, but in her offspring as well.

This is extremely important information as it clearly demonstrates that environmental factors, which in this case was diet, can dramatically influence the function of genes epigenetically without ever modifying what is written in the gene.

### **Barker's Thrifty Phenotype Hypothesis**

In 1986, studies by David Barker of the University of Southampton, led to him to being able to determine that of the 15,000 people born before 1930 in six villages in Hertfordshire the following statistics could be obtained:-

- 3,000 were dead, almost half from heart disease, and a disproportionate number of these deaths were in people who weighed less than 5 pounds at birth.
- At 1 year old, the rate of heart disease in men who weighed 18 pounds or less was three times that of those who weighed 27 pounds or more.

This information allowed Barker to hypothesize that in bad conditions a pregnant female is able to modify the development of her unborn child so that when it is born, it will be programmed for survival in an environment where resources are short. He named this phenomenon "The Thrifty Phenotype".

In a nutshell, if you have developed in utero with a Thrifty Phenotype, and live and grow in an affluent environment, the evidence shows that you may be more prone to disorders such as diabetes, whereas those developed *in utero* having received a positive maternal forecast will be adapted to good conditions and therefore be in a better position to cope with rich diets.

Dozens of later studies have been conducted and all of them have convincingly demonstrated a powerful link between low birth weight and an increased risk of developing chronic medical disorders decades later. It is an alarming fact that most doctors are completely unaware of this important fact.

Both poor prenatal and poor early postnatal nutrition can invoke changes in later life for the unborn child which can invoke the following changes in later life:-

- Changes in the profile of the variety of enzymes made by the liver
- The composition and ratios of the blood lipoproteins
- Clotting factors in the blood
- The uptake of glucose by the organs of the body
- The filtering capacity of the kidneys
- The hormone responses to stress
- The ability of insulin to signal the cells properly and the levels of leptin, a hormone that plays a key role in regulating energy intake and energy expenditure including the regulation of appetite and metabolism

If you put all of this information together you end up with the following diseases which are prevalent in western society and all of which have been shown to be increased in low birth weight babies:-

- Coronary heart disease
- Stroke
- Type 2 Diabetes
- Metabolic Syndrome (Syndrome X)

### Neel's Thrifty Genotype Hypothesis

Barker's Thrifty Phenotype Hypothesis owes much to the work of James Neel from studies he conducted in the 1950's and 1960's. Neel developed a theory which he called the Thrifty Genotype Hypothesis following work principally with haemoglobin and sickle cell anaemia, but also with blood groups as genetic markers and studies of radiation effects of the Hiroshima and Nagasaki bomb blast survivors. His hypothesis put forward the general idea that certain genes in humans have evolved to maximise metabolic efficiency and food handling behaviour. However, in times of abundance, these genes predispose their carriers to diseases caused by excess nutritional intake, such as obesity.

Neel's work was published in 1962 and his "thrifty gene" hypothesis explained the tendency of certain ethnic groups to develop obesity and diabetes. His studies included the population of the small Pacific island of Nauru and the Pima Indians of Arizona, USA. Both had seen massive lifestyle changes over the past two centuries and both had seen huge rises in the frequency of Type II Diabetes. Their lifestyles had changed from the hunter/gatherer and subsistence agriculture to sedentary occupations and consumption of energy-dense foods. Neel reasoned this caused some sort of genetic-environment disconnect, which in times of nutritional deprivation conferred a survival advantage, but at times of adequate or over-nutrition caused detrimental effect to the system. It follows from his theory that a history of food scarcity in ethnic groups will have caused them to have undergone a relatively high evolutionary pressure and hence, they may harbour more thrifty genes than other populations.

The thrifty genotype and the thrifty phenotype hypotheses therefore assume that some people can be genetically programmed for scarcity and metabolically biased in such a way that during famine their survival is favoured, but when placed in an affluent environment, they succumb to disease.

### SUMMARY

So the concept of the term "Predictive Adaptive Response" is quite simple. Critical interactions that can go on to determine the future health and wellbeing of an individual, occur before birth as our genes interact with the environment during the process of fetal development. In essence, the fetus judges the environmental conditions that it expects to encounter in its future life from the nutritional environment that it receives from the mother *in utero*. The children of the Dutch parents of the "Hungerwinter" were genetically programmed to expect a life of a continued limited calorie environment. However, in post-war Holland when normal calorie intake resumed to typical Western standards, their bodies were not programmed or prepared for it and so they developed what are now commonplace Western diseases including; type 2 diabetes, obesity and artery disease.

The so called "age of plenty" that we now live in, has become the root of our many health problems. Most health experts agree that the UK is facing a huge increase in the number of people with diabetes. Since 1996 the number of people diagnosed with diabetes has increased from 1.4 million to 2.9 million. By 2025 it is estimated that five million people will have diabetes. Most of these cases will be Type 2 diabetes, because of our ageing population and rapidly rising numbers of overweight and obese people<sup>(2)</sup>.

China and India is an even more worrying time-bomb waiting to explode. Their thrifty phenotypes which have developed over the course of many generations will collide with the introduction of western diets into their massive populations. In 2010, David Gutierrez a staff writer from NaturalNews.com reported the following:-

*"China suffers from far more cases of diabetes than previously thought, placing its diabetes epidemic on the same scale as that of the United States, according to a study published in the New England Journal of Medicine.*

*'In the last 10 years, with the country's economy expanding quickly and people's standard of living improving, people's lifestyles have changed," said co-author Yang Wenying of the China-Japan Friendship Hospital in Beijing. "China's economic development has gone from a situation of not being able to eat enough, of poverty, to having enough food and warm clothes, and doing much less exercise.'*

*Lifestyle changes such as increased urbanization and sedentism and 'Western' diets high in fat and junk food have caused an increase in heart disease, diabetes, cancer and other 'lifestyle diseases' across China. According to the new findings, there are 92 million diabetics in China, more than twice as many as the 43.2 million recently estimated by the International Diabetes Federation (IDF). Another 150 million are believed to be pre-diabetic.*

*This means that 10 percent of Chinese residents are diabetic, while 16 percent are at risk of developing the disease."<sup>(3)</sup>*

If these statistics are expanded across the world, the sheer numbers along with their resistance to cost-effective treatment does not bode well for the future.

As natural healthcare practitioners, I believe it is our duty to try to influence nutritional requirements for mothers in both prenatal, *in utero* and post natal areas. As a father of four children, and being introduced to nutritional advantages some three years before my first child was born, I always ensured good quality nutritional supplements was part of their mothers daily routine.

For those of us who are not pregnant or less than one year old we also need to improve our genetic heritage. So what do we do?

Once a human body passes it's mid-twenties, it rapidly loses it's plasticity which is the property of a body to undergo permanent change when subjected to some sort of influence. The body rapidly moves from the growth phase into the static stage. So it is important to have a plan which should be less about trying to engineer epigenetic changes and more about determining the range of your body's predictive adaptive response, so that a lifestyle is designed that allows the body to function within its limits.

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