The photo shows a group of healthy New Zealand teenagers in their first term of Year 9. They have reached puberty, are embarking on secondary school and have hopes and aspirations for their futures. What will their futures hold? What will contribute to their happiness, health, potential and success as adults? What factors will they have control of and what factors influencing their future are beyond their control? Genetic inheritance, family, resources, friends, education, social connections, health, and economic situation will all influence their futures. They will make choices about life style and education as adolescents and young adults that will influence the direction of their lives. If they choose to live active healthy lives and say no to high fat diets, drugs and alcohol, they will reduce their chances of disease in adult life and improve their potential to live full, active and productive lives. If they select to pursue educational opportunities offered to them they will develop their intellect, may gain qualifications and improve their adult income potential, and with this their potential to support their families. If they maintain their family, social and cultural connectedness they will develop essential social support networks that contribute to health and well being.

But is it that simple? Do individuals have total control over their potential well being? No. Genetic inheritance means that it is not that simple. Our well being is intrinsically linked to the genes that we have inherited and the interaction of these genes with our environment, including the life style we choose to impose on our genes! We know that some people inherit genes that give them a propensity for certain diseases. Diseases such as type 1 diabetes and cystic fibrosis are the result of inheritance of alleles specific to these conditions. Some genes are associated with increased likelihood of disease. BRCA-1 and BRCA-2 for instance are genes that if inherited in a certain form increase likelihood of breast cancer, accounting for about 10% of breast cancers. The environment that we expose ourselves to also counts. If we choose to eat a high fat diet it is likely we will become obese and increase our chances of diseases such as heart disease, strokes and type II diabetes.

Scientists at Auckland University’s Liggins Institute have shown that in addition to environment during adulthood impacting on likelihood of disease, the environment that we are exposed to in the womb can alter our metabolic pathways and increase our likelihood of suffering from a number of adult diseases. The diet that a woman eats during pregnancy can affect the health outcomes of the fetus from childhood through to adulthood. Maternal undernutrition during pregnancy leads to increased chances of early onset puberty, a preference for fatty foods, reduced adult physical activity, polycystic ovaries, infertility, obesity, heart disease, high blood pressure, and type II diabetes in adulthood. Maternal high fat diets also increase the risk of adult disease. Scientists are currently exploring why this happens and predict that it may be a result of epigenetic change. Moreover, it has now been clearly demonstrated in animal models that some changes in phenotype caused by epigenetic modifications can be passed on to the next generation—challenging the notion that environmental effects on phenotype cannot be inherited by the next generation.

A Poor Fetal Environment Leads to Increased Risk of......

- Learning
- Early Puberty
- Adult Disease

There is clear scientific evidence that a number of adult diseases have their origins before birth. The challenge for scientists now is to understand WHY this happens. Understanding WHY can potentially lead to THERAPY and INTERVENTION.
The Evidence

Ethically it would clearly be inappropriate to carry out a study on humans where women were deliberately deprived of food during a pregnancy. Sadly there are some unfortunate periods in recent human history where war has resulted in this happening. The Dutch Hunger Winter during 1944—1945 is one such time. During this period Germany was occupying the Netherlands and banned the transportation of food from the agricultural regions in the north to the urban areas in the west. A severe famine resulted for nine months with people in the west getting only 400—800 calories a day instead of the normal 1800. The children born to mothers who were pregnant during this time have been followed and found to have very high rates of hypertension (high blood pressure). This is believed to be a result of the fetus sending all available energy to the brain, resulting in the child being born with kidneys that have fewer nephrons than normal, leading to high blood pressure. These people are also more likely to be obese.

Other evidence from humans has been gathered by looking at historical data about health and disease in populations. These are epidemiological studies that involve collection of data to compare adult health status to health data collected at birth such as birth weight, placental weight, body length and proportions. Professor David Barker and his colleagues presented extensive data in the 1990’s demonstrating that there is a relationship between low birth weight and increased likelihood of adult disease such as heart disease and type II diabetes (Fig 2).

Further supporting evidence from the Raine Study in Western Australia showed that girls who entered puberty earliest were smaller than their peers at birth and fatter than their peers when they were 8 years old (Fig 3). This study started in 1989 and followed 3000 pregnant women and their children. Scientists throughout the world are interested in understanding this concept which is referred to as the “fetal origins of adult disease”. Animal studies are used to model this phenomenon in order to study the effect at a molecular level. The first step is to establish that the response seen in humans can be unequivocally shown in the animal model. This ensures that the genetic evidence can be trusted. Scientists at Auckland University’s Liggins Institute have shown the offspring of rats undernourished during pregnancy are likely to become overweight when fed a healthy diet and are more likely to prefer a high fat diet and low activity levels (Fig 4). They also have high blood pressure, enter puberty early, and show an increased tendency to develop type II diabetes. These scientists have also shown that rats overnourished during pregnancy will enter puberty early and become overweight on a balanced diet, leading to increased chance of adult diseases such as high blood pressure and type II diabetes.

Programmed for Obesity

In addition to being programmed for obesity, animals undernourished in the womb are also programmed for high blood pressure, insulin resistance (leads to Type 2 Diabetes), early puberty, low activity levels and overeating.

The blue striped bars on the graphs show that rats who were undernourished in the womb and put on a balanced (control) diet when born are more likely to eat more and exercise less as adults.

The pink solid bars show that rats who were undernourished in the womb and put on a high fat diet when they were born are even more likely to eat more and exercise less.
Developmental Programming—The Predictive Adaptive Response Theory

The prenatal environment is having an effect on adult phenotype.

Professor Peter Gluckman of the Liggins Institute and Professor Mark Hanson of the University of Southampton have proposed that the events that scientists have observed are due to a mismatch between the environment that the fetus experiences in the womb and the environment that the child experiences once born. In the womb the fetus has experienced “hard times” (i.e. there is not enough food) and will make a series of metabolic adaptations in order to survive. As a result of this the fetus is well adapted for a life of undernutrition. When it is born into a world where there is plenty of food, the child is not well adapted. This can result in a series of potential problems including obesity, diabetes, heart disease and early puberty.

Environment, phenotype, survival, and evolution.

The concept of “survival of the fittest” suggests that animals that are best adapted to an environment as a result of the genes that they have inherited are the ones that will survive to reproduce, and therefore pass their “best fit” genes on to the next generation. The alleles that are “selected for” will become more common in the population, increasing the proportion of these alleles in the gene pool, and improving the survival potential of the population.

The environment that an organism experiences impacts on its phenotype. The NZ mangrove, Avicenna marina var. resinifera is an example of this. In Northland the mangroves form tall intertidal forests whereas in the Bay of Plenty, the same mangrove species will grow to only 0.5m in height. Mangroves will not grow at all further south where it is colder. While a mangrove transplanted from Tauranga to Waitangi would grow taller in the warmer environment, some environmental impacts on genes are more complex that this and result in permanent changes to the phenotype. An example is temperature dependent sex determination seen in many reptile species. This adaptation is believed to have evolved to reduce interbreeding amongst offspring of the same parents. The Tuatara will produce mostly males from eggs incubated in nests at higher temperatures (21-22°C) and females at lower nest temperatures.

We know from examples in nature that some animals are capable of predicting their adult environment and adjusting their phenotype during development to ensure they are well adapted for the predicted adult environment, improving survival. These animals demonstrate a PREDICTIVE ADAPTIVE RESPONSE. An example of this is the meadow vole, a small animal (similar to a mouse) found in Alaska, Canada and the Northern United States. With a life span of around 6 months, the meadow vole will experience either summer or winter conditions in its life—not both. Coat thickness is determined before birth by maternal signals involving melatonin, related to whether the day length is shortening or lengthening. The temperature that the meadow vole experiences before birth and in the nest is similar, so the predictive advantage of choice of coat thickness will not be seen until the vole moves from the nest and experiences either summer or winter temperatures, depending on the time of the year that it was born. Meadow voles born at a time when they will live through winter develop a thick coat, whereas those born to live during summer will develop a thin coat. This is an example of DEVELOPMENTAL PLASTICITY.

The phenotype is being determined by a combination of genotype and environment, determining which genes are turned on to produce the phenotype most suitable for the predicted environment.

Developmental plasticity offers a survival, and therefore evolutionary advantage if the predicted environment matches the actual adult environment as in the case of the meadow vole. However, what we have seen in the evidence relating to fetal origins of adult disease is a mismatch between predicted environment and actual adult environment. When there is this mismatch, problems occur and the results of the plasticity are animals that are maladapted to their environment and therefore have reduced chances of survival for the individual. The animals that experienced poor fetal nutrition are programmed to have increased chance of adult disease.

These changes in phenotype are permanent, yet they do not change the genotype. It is likely that these changes in the phenotype have been made in order to maximise the potential of the individual to survive. The fetus is predicting that the environment into which it will be born will match the environment in which it is developing. It is developing in a way which will best fit the environment, maximising its potential to survive and reproduce. Scientists believe that there are probably only some stages during development where the environment is capable of influencing the phenotype in this way. During these stages, we say the development is very “plastic”, it is mouldable. In early life when the differentiation of cells into specialised tissues is not complete, there tends to be a high potential for plasticity.
Gene Environment Interactions and Evolution

The Central Dogma of Biology describes the relationship between DNA, RNA and proteins. The genotype of an organism, found in the DNA is expressed when genes are turned on and proteins are synthesised. In order to be expressed, a gene must be unpacked from the condensed state in which it sits wrapped around histone proteins within the chromosome (the DNA—Protein complex is chromatin). This allows the transcription factors access to the gene so that the process of transcription can occur.

In some gene-environment interactions, a process called **EPIGENESIS** is occurring. This process involves non-genetic factors that do not change the genes themselves but can change the behaviour of the genes. These factors can change the ability of a gene to be accessed within the chromatin and expressed. Epigenetic factors can include changes to the chromatin structure or the addition of methyl (CH₃) groups to the DNA (methylation). **Scientists know that environmental influences early in life in a number of organisms cause epigenetic changes to the DNA and therefore change the phenotype, without changing the sequence of bases in the DNA.** There is evidence that the packaging of the DNA in the chromosome is changed. This alters the ability of the gene to be unpackaged and transcribed, therefore changing the phenotype. Evidence suggests that the responses seen in the individuals who experienced poor fetal nutrition and increased likelihood of adult disease are caused by epigenetic changes to the DNA. If this is found to be correct, the poor fetal environment is causing an **EPIGENETIC** change in the DNA packaging which is altering the ability of specific genes to be expressed and therefore altering the phenotype.

A number of human and animal studies have suggested that epigenetic **effects may be passed on to the next generation**, despite the fact that there is no change in the sequence of the DNA. In 2006, scientists showed that epigenetic changes could be passed on to the next generation using a mouse model and investigating the agouti coat colour gene (Conney, 2006).

The inheritance of coat colour in the Agouti mouse is well known as an epistatic inheritance pattern resulting from interaction of genes on 3 different loci. The Agouti allele (A) is dominant over the non-agouti (a). The full colour allele (C) is dominant over the albino allele (c) and the Black allele (B) is dominant to the brown allele (b). The agouti gene also controls appetite.

A number of variations in the Agouti gene exist including A=agouti, A--=lethal dominant yellow and A+=viable yellow.

Genes A, B and C show epistatic interaction. No colour is developed unless the dominant C allele is present in the genotype. Scientists crossed mice carrying the A+/a alleles (striped-obese) with mice that were aa (black-lean). They found that the offspring of these mice had a range of phenotypes from agouti-lean brown, to striped-obese, and yellow-obese. This range of phenotype is a result of epigenetic interactions. The more DNA methylation that occurs in the A+/a allele, the more lean-brown and the less-obese yellow offspring there will be in the litter.

Supplementing the mother’s diet with vitamin B12, folic acid, choline, and betaine will increase the level of methylation on the gene. These supplements are known as methyl donors. Offspring of both mothers and grandmothers who had been fed supplemented diets were more likely to be lean-agouti brown mice and less likely to be yellow or striped-obese mice. The fact that the supplemented diet could be that of the mother or the grandmother shows that the methylation effect is being passed onto the next generation—the diet is affecting the germ line developing in the F₁ generation and these effects are being carried through to the F₂ offspring.

**Most epigenetic changes are not on.** However evidence that some epigenetic modifications caused by environment that change phenotype are passed on via the gametes now exists and challenges traditional evolutionary thinking.  

![Fig 7: Epigenetic processes such as methylation can prevent transcription, changing the phenotype.](image)

**Fig 8: Adapted from Conney (2006).** P1 generation—Female mice (a/a, black) are mated with male mice (A+/a, pseudoagouti or mottled). Female mice are fed either a control or a methyl-supplemented diet. All other mice receive control diet. Pseudoagouti females (A+/a) of the F₁ generation are mated with a/a, black males to produce the F2 generation. Both the F1 and F2 generation mice from methyl-supplemented P1 females show a greater degree of agouti coat colour than F1 and F2 generation mice from control diet P1 females.

**Further Reading:**

Gluckman P and Hanson M (2007) **Mismatch: Why our world no longer fits our bodies** Oxford University Press


The authors would like to thank the Year 9 students of Tamaki College in Auckland (2007) for the use of their photo.

**For further information contact** Jacquie Bay, j.bay@auburn.ac.nz; Deborah Sloboda, d.sloboda@auburn.ac.nz

Copyright © Liggins Education Network for Science, 2008  http://LENS.auckland.ac.nz