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Our children are the guardians of our genome

Health and wealth of future generations relies on what priorities we give them today

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1 Summary

Our Children are the guardians of our genome

Health and wealth of future generations relies on what priorities we give them today

Evidence has been mounting over several decades but more strikingly from genomics research in the last decade about the importance of gene-environment interactions especially in pregnancy and childhood. Knowledge about how the wider environmental factors are 'turning the genes on and off', the new science of epigenetics, is gaining a wider coverage and influence. Research has demonstrated that genes and the environment are not mutually exclusive but is inextricably intertwined, one affecting the other. Evidence in mammals is showing that these gene switches (changes or markers) can be passed on to multiple future generations when they affect pregnant mothers and their offspring at pre-puberty and they can also be reversed. The reversibility of these gene markers gives health prevention a new and reinforced emphasis but no more so significantly than in pregnancy and childhood in humans.

It has never been so clear that to ensure a better future health for our children, grandchildren and future generations we should give children our priorities in everything we do. Positive preventive actions in pregnancy will not only improve the health of the pregnant women and their babies but also their babies' babies at once as mothers act as 'the incubators of future generations'. Also, positive preventive actions during childhood development period from birth, in nurseries and in schools are the most important and cost effective time to intervene and prevent diseases in this generation as well as influencing future generations by the same actions.

Epigenetics research is at the forefront of a paradigm shift in scientific thinking. It is changing the way the causes of diseases are viewed, as well as the importance of lifestyles and environmental influence. Furthermore there is increasing evidence that early life exposures of fathers, mothers or ancestors can contribute biologically to developmental variation in the offspring. Transgenerational inheritance or, as some scientists refer to as responses, may be for better or worse. Research findings on mammals has demonstrated that adverse or enriched environments have responses over 3-7 non-exposed generations. The genome is continually surprising biologists with how fast and fluidly it can change gene expression — and thus the phenotype.

What epigenetics evidence suggests

- Changing the environment and improving life style factors not only improve health outcomes but are actually shown to switch on genes that are protective and switch off genes that are deleterious.

- If we do the above in pregnancy and childhood not only we achieve the outcomes as described above but we will be impacting three generations with those actions and some scientists are predicting more than three generations.

- Positive preventive actions are required during childhood development not just at the first 1000 days of life but also later on in childhood especially at pre-puberty period, a period of great phenotypic plasticity and transgenerational influence.

- A multigenerational perspective to public health research, practice and policy is required

We know that health of children directly influence children's educational attainment and that education also directly influence future health outcomes. Therefore a strategy of sustained synergistic actions on both children's health and education whereby one strengthens the other is the best way forward. A cultural shift in our society mediated through an integrated approach by governments, organisations, society and families is required whereby we prioritise 'our insurance policy' for better future by prioritising our children.

We need to raise the bar of what we consider a high quality standard starting from the selection and training of NHS staff delivering care in pregnancy and childhood as well as staff involved in child care and development in nurseries and teachers, head teachers in schools education system, to those managing services provided by health and educational systems. Schools become safe heavens and the safety net for children but especially children from poorer background as they receive similar high standards of education and health and well being care as that received in more affluent areas of Wales. Health workers, especially those who work with mothers to be and children, and staff working in education need an understanding of the generational implications of lifestyle and the wider environmental factors on the health and well being of children and build this into their everyday working practice.

Various policies we have adopted over the years to reduce inequalities in health have failed to dent the records as the gap continues to increase.

The argument is so crucial for sustaining future generations in Wales that this report advocates for enshrining the prioritisation of children in law. This can be achieved either through extending the powers of the UN Convention on the Rights of the Child as enshrined by Welsh Government based on adopting the UN CRC as the basis of all their work for children and young people. The WG seven core aims for children and young people could be extended to include a statement of intent to place children's health, education and wellbeing, from conception as the first priority for public policy to sustain future generations in Wales. Or this could be achieved by enshrining it within the Well-being of Future Generations (Wales) Act 2015.

Only a strategy of sustained integrated actions on both health and education for children over several decades would have the best hope of:

1. Improving the health of the nation
2. Reducing inequalities in health
3. Improving social mobility
4. Improving the economy
5. Reducing the impact of child poverty

2 What needs to change in public health policy in Wales?

2.1 We should place maternal and child public health actions as the first and the most important of all public health priorities **and this should be the basic principle for all future strategies for at least the next two decades.**

2.2 **We need to develop a new vision based on the principle of 'Sustained synergy of Intertwined Actions on Both Children's Health and Education'.** This will help us to achieve our desired aims of improving the health and wellbeing of the next generations and reducing inequalities in health. The combined actions on health **at all stages of childhood not just early years** intertwined with actions on child development and education both planned and delivered in a synergistic way will exponentially improve the outcomes. The total outcomes will be more than the sum of health plus education as one strengthens and reinforces the other. This highly achievable aim is facilitated by our legitimate access to those whom we need to help and influence, i.e. pregnant women and children through antenatal care, play groups, nurseries and schools.

2.3 Advocating for the extension of the United Nations Convention on the Rights of the Child (UNCRC) which was adopted by the Welsh Government in 2009 as the basis of all their policy making for children and young people. The extension should include **a statement of intent to place Children's health, education and wellbeing, from conception as the first priority for public policy to sustain future generations in Wales.** Or this could be achieved by enshrining it within the Well-being of Future Generations (Wales) Act 2015.

2.4 Such a vision could complement and strengthen various Wales initiatives such as flying start; healthy schools Scheme; Communities First; Integrated Family Support Services; various breast feeding initiatives; maternity smoking cessation programmes and other programmes aimed at improving parenting skills in Wales.

3 Why we have to prioritise children's health from conception until puberty?

3.1 What is epigenetics?

It is the study of changes in gene expression, without changing the underlying DNA sequence, and these changes can be inherited. The name *epi-* (Greek: *επί*) means over, above, in addition to g*enetics.*

Others define epigenetics as 'the science of enduring, but ultimately reversible, changes in the pattern of gene activity, during embryo development and beyond, that do not involve alteration of the DNA sequence. These changes occur in response to environmental changes or conditions within the embryo and more generally'.

Epigenetic regulation of gene expression is a key element in development and how we respond to the environment during our life course. Mechanisms of epigenetics modifications includes DNA methylation that effect genes, histones modifications, which are the protein structures that form major part of the chromatin in the nucleus acting as spools around which DNA winds and several other mechanisms. Methylation of DNA is the mainstay of cellular memory with methylation patterns being reinstated in daughter cells after cell division. This enduring nature of epigenetic change probably underlies many of the lifelong health impacts of foetal and childhood experiences. Furthermore there is increasing evidence that early-life exposures of fathers, mothers or ancestors can contribute biologically to developmental variation in the offspring. These transgenerational responses may be for better or worse, so a multigenerational perspective to public health research and practice will be important (*Professor Marcus Pembrey, Personal Communication*). Epigenetics in the last decade or two is changing the way scientists look at genetic inheritance.

The science behind this mechanism has been building steam for decades. Research has demonstrated that genes and the environment are not mutually exclusive but are inextricably intertwined, one affecting the other.

Details of the evidence from epigenetics science are in Appendix 1.

4 Summary of the scientific evidence on epigenetics

Many diseases and conditions are linked to epigenetic. So far, scientists have been able to link obesity and insulin resistance and many diseases such as: heart disease; various cancers; autism; neurodegenerative disorders; bipolar disorder; schizophrenia; atherosclerosis; hypertension; SLE; kidney diseases; asthma and many rare genetics disorders such as Fragile X syndrome. Evidence compiled from various studies are summarised here.

- **Smoking, child abuse and socio-economic position**

In the **1958 British Birth Cohort study the** DNA was found to carry distinct DNA methylation patterns associated with child socio-economic position (SEP)[1], prenatal tobacco exposure and child abuse[2]. The methylation signature of early-life SEP in adult blood DNA taken at 45 years is consistent with epigenetic mechanisms contributing to the association between early-life SEP and adult health.

Studies of hippocampus from suicide victims who had known histories of childhood abuse showed higher methylation when compared with those who were not abused[3].

- **Diet, obesity, exercise and diabetes**

An association was found between lower consumption of carbohydrates during early pregnancy and the activity of a gene thought to be linked to increased fat levels in children. Researchers found that mother's diet during pregnancy may influence the risk of obesity in her child in later life[4]. They found that epigenetic changes in the DNA of children at birth allowed researchers to predict their body weight later on in childhood. It explained 25% of the difference in the fatness.

Another study had revealed that the **patterns of epigenetic modifications in monozygotic twin pairs diverge as they become older as** approximately one-third of MZ twins harbored epigenetic differences in DNA methylation and histone modification.

A lot of research has also been done to **elucidate the complex etiologies of both obesity and type II diabetes (T2D)**. For many years, the most effective preventative treatment suggested for both obesity and T2D is exercise and a healthy diet. Research has now shown that exercise alone is sufficient to change our epigenome and possibly our destiny. A study was carried out of men who were typical coach potatoes who participated in 1.8 hour spinning sessions per week without changing their diet and followed up for 6 months. As well as a decrease in waist-hip ratio, which was also associated with increased methylation of a gene previously associated with waist-hip ratio[5], significant methylation changes were observed in 18 candidate genes previously associated with

obesity and 21 genes associated with T2D. This study highlights the **importance of exercise in improving overall health**. Doing as little as two hours of aerobics a week will not only improve your fitness; it can also decrease the risk of obesity and T2D.

Both mice and human have the agouti gene, when it is completely unmethylated the mouse has yellow coat colour, is obese and prone to diabetes and cancer. When the agouti gene is methylated (as in normal mice) the coat colour is brown and the mouse has a low disease risk. Fat yellow mice and brown skinny mice are genetically identical. When researchers fed pregnant yellow mice a methyl rich diet, most of the resulting pups were brown and healthy and stayed that way for life.

More recently researchers have also found that **the age of DNA methylation of blood predicts all-cause mortality in later life[6].** DNA methylation of accelerated ageing are heritable traits that predict mortality independently of health status, lifestyle factors, and known genetic factors. A 5-year higher difference between chronological age and methylation age (Δ_{age}) is associated with a 21% higher mortality risk, adjusting for age and sex. After further adjustments for childhood IQ, education, social class, hypertension, diabetes, cardiovascular disease, and *APOE* e4 status, there is a 16% increased mortality risk for those with a 5-year higher Δ_{age}. A pedigree-based heritability analysis of Δ_{age} was conducted in a separate cohort was found to be 43%.

- **Transgenerational epigenetic observations and inheritance in mammals**

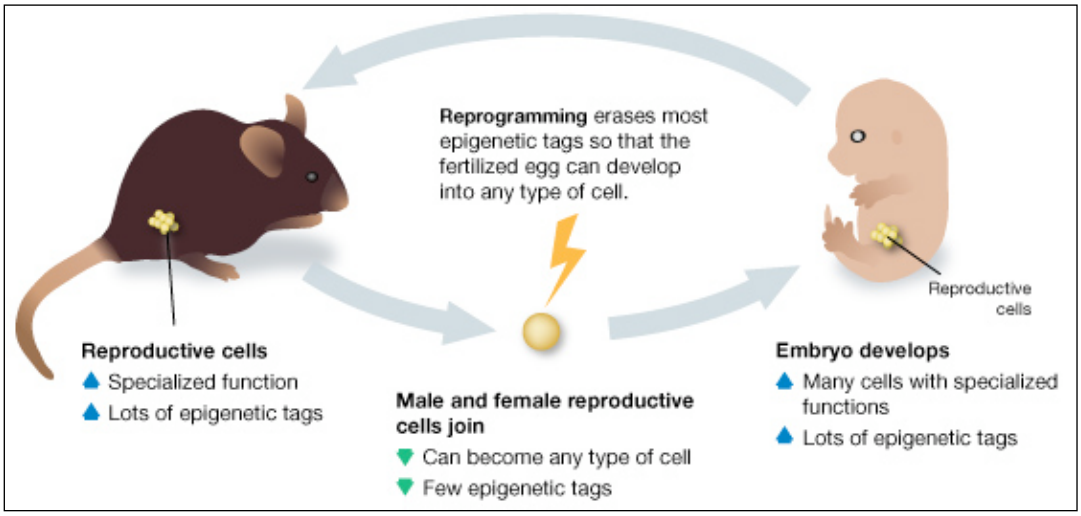
The phenomenon is nicely illustrated on University of Utah Genetics Science Learning Centre Website. We used to think that a new embryo's epigenome was completely erased and rebuilt from scratch. But this isn't completely true. Some epigenetic tags remain in place as genetic information passes from generation to generation, a process called epigenetic inheritance.

Epigenetic inheritance is an unconventional finding in recent years. It goes against the idea that inheritance happens only through the DNA code that passes from parent to offspring. It means that a parent's experiences, in the form of epigenetic tags, can be passed down to future generations.

Most complex organisms develop from specialized reproductive cells (eggs and sperm in animals). Two reproductive cells meet and then they grow and divide to form every type of cell in the adult organism. In order for this process to occur, the epigenome must be erased through a process called "reprogramming."

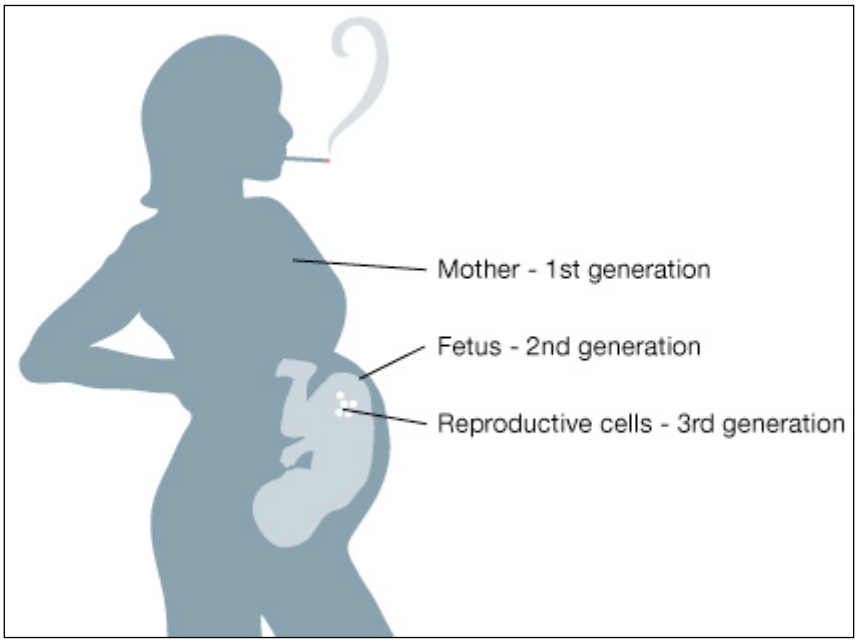
Reprogramming is important because eggs and sperm develop from specialised cells with stable gene expression profiles. In other words, their genetic information is marked with epigenetic tags. Before the new organism can grow into a healthy embryo, the epigenetic tags must be erased.

At certain times during development (the timing varies among species), specialised cellular machinery scours the genome and erases its epigenetic tags in order to return the cells to a genetic "blank slate." Yet, for a small minority of genes, epigenetic tags make it through this process and pass unchanged from parent to offspring.



Source: University of Utah Genetics Science Learning Centre Website

Reprogramming resets the epigenome of the early embryo so that it can form every type of cell in the body. In order to pass to the next generation, epigenetic tags must avoid being erased during reprogramming[7].



Source: University of Utah Genetics Science Learning Centre Website

Three generations at once are exposed to the same environmental conditions (diet, toxins, hormones, etc.). In order to provide a convincing case for epigenetic inheritance, an epigenetic change must be observed in the 4th generation[8].

Biologists first observed this 'transgenerational epigenetic inheritance' or some scientists call it epigenetics transgenerational responses, in plants. But, over the past few years, evidence has been accumulating that the phenomenon occurs in rodents and humans as well.

An experimental study from Emory[9] in USA found that lab rats conditioned to fear a certain smell will pass that fear on to their children. Mouse pups — and even the offspring's offspring — can inherit a fearful association of a certain smell with pain, even if they have not experienced the pain themselves, and without the need for genetic mutations.

A study from Washington State University showed that environmental toxins can cause inherited diseases[10]. They found that exposure to an environmental toxin during embryonic development can cause an animal, and almost all of its descendents, to develop adult-onset illnesses such as cancer and kidney disease. Their discovery suggests that toxins may have played a role in the rapid increase in localized geographic areas of diseases that were previously thought to be caused primarily by genetic mutations. The effect persisted through four generations, with about 85 percent of the offspring in each generation developing conditions such as breast tumors, prostate and kidney diseases, immune system abnormalities, and premature aging.

These findings raise the possibility that **environmental factors may play a much larger role in evolution than has been realised before**.

In rats, maternal grooming behaviour effected glucocorticoid receptor expression in the brain of their offspring. High grooming mothers produced less fearful offspring who showed better physiological stress control[11].

Another study from the Los Angeles Biomedical Research Institute showed that **if pregnant rats are exposed to nicotine, not only will their offspring develop the asthma induced by this drug, so will the offspring of those offspring[12]**.

- **Transgenerational epigenetic observations and inheritance in humans**

In an observational study that was conducted in Sweden utilising historical records, including harvests and food prices, in an isolated municipality, Överkalix, 303 probands born in 1890, 1905, or 1920, and their 1,818 parents and grandparents were studied. This transgenerational inheritance was observed with exposure during the slow growth period (SGP). The SGP is the time before the start of puberty,

when environmental factors have a larger impact on the body. This occurred in the SGP of both grandparents, or during the gestation period/infant life of the grandmothers. Females experienced a twofold higher mortality if their paternal grandmother had good food availability during SGP. Paternal grandfather's food supply was only linked to

mortality rates of grandsons, while paternal grandmother's food supply was only linked to mortality of granddaughters. Grandsons of Overkalix boys who had overeaten died an average of 6 years earlier due to cardiovascular diseases than the grandsons of those who had endured a poor harvest. When controlled for certain socioeconomic variations, the difference in longevity increased to an astonishing 32 years! If food was plentiful, then diabetes mortality in the grandchildren increased. Women lived shorter lives on average if their paternal grandmothers experienced famine during pregnancy. A single winter of overeating as a youngster could initiate a biological chain of events that would lead one's grandchildren to die decades earlier than their peers did.

Also **observational studies of the effects of famines in Holland in the 1940s, in China in the 1950s and in the United States** over a century ago showed that they changed the lifespan and obesity rates in subsequent generations. Researchers proposed that these famines switched on genes that increased the accumulation of body fat in times of plenty, in order to improve survival chances in times of famine. With calorie-dense fast foods more freely available now than at any time in history, the seeds of the current obesity epidemic may thus have been sown in the 19th century. The risk of obesity they proposed can come not just from your own environment or your mother's but higher up the ancestral chain.

In the Avon Longitudinal Study of Parents and Children (ALSPAC) (Children's of the 90s) a cohort of 14,000 pregnant women in 1991-2 were followed as well as most children and fathers ever since. Fathers who smoked as pre-adolescents have increased their sons BMI at 9 years of age, but not their daughters[13].

Women who suffer higher levels of stress while pregnant are more likely to have children with lower IQs due to lower cognitive skills that was independent of family attributes that categorise post natal environment and they also had greater emotional difficulties[14,15].

Transgenerational inheritance of more than 3 generations in man is a totally new concept although accepted as probably happening in man but there are disagreements about the mechanisms of it, other scientists disagree about the extent and the degree.

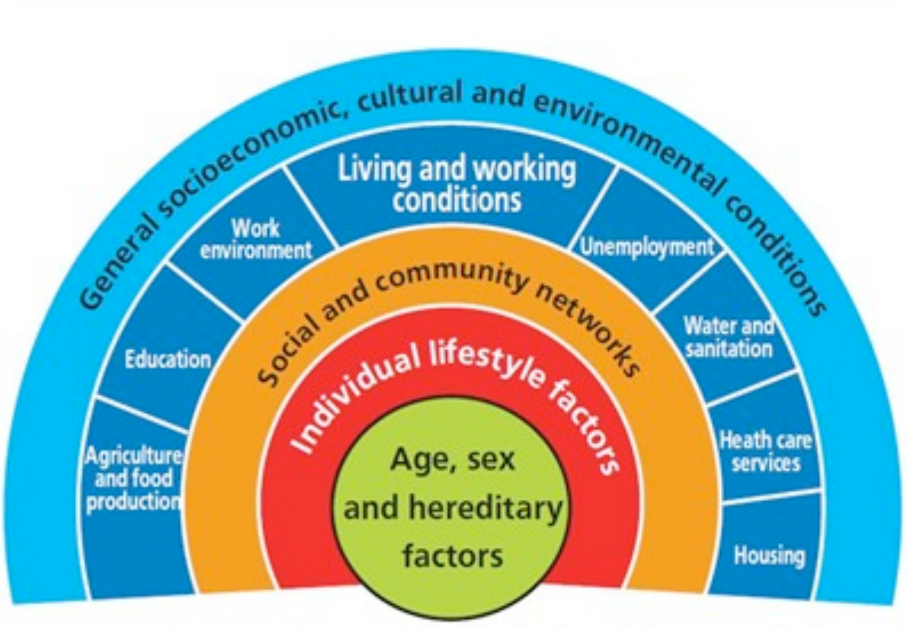
5 What are the public health implications of epigenetics scientific findings?

Dahlgren and Whitehead's 1992 representation of the wider determinants of health is still stands as the most effective illustration of health determinants and continues to inform the work of those concerned with understanding and reducing the health inequality gap.

Age, sex and hereditary factors in Dahlgren and Whitehead's model personal characteristics (such as age, sex, ethnicity and constitutional factors (e.g. genetic, biological) occupy the core.

These factors are highly significant for health, yet they were and continue to be largely seen as stable factors and factors that are beyond the reach

and influence of public health improvement strategies, policies and practices. However, other factors that can be influenced by public health strategies extend out in layers from the model's core.

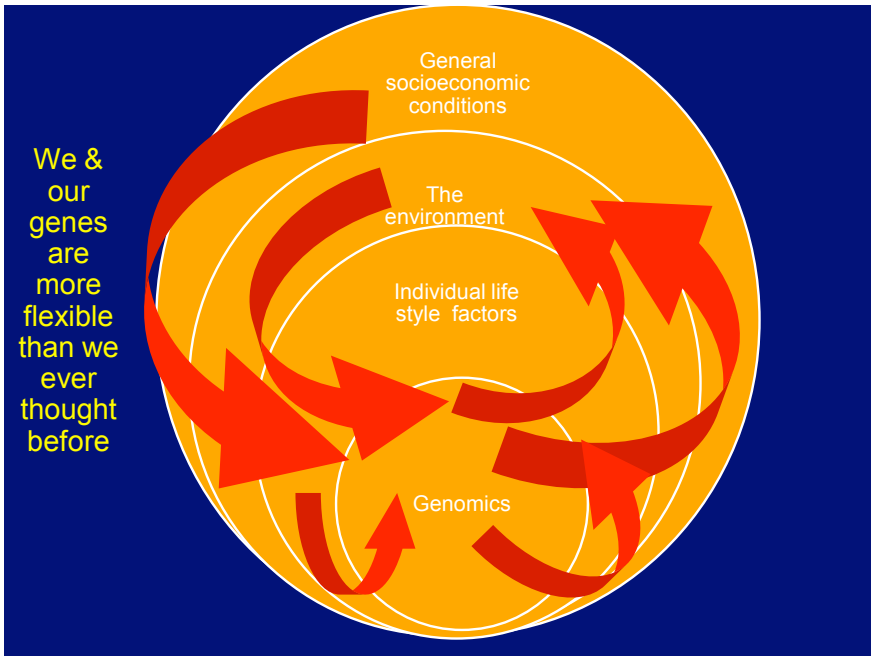


The Determinants of Health (1992) Dahlgren and Whitehead

Epigenetics research findings, as described in this report, show very clearly that although the DNA within the genes we inherit are stably inherited from one generation to the next bar random mutations, both the environment at large and individual lifestyle can also directly interact with the genome to influence epigenetic phenotypic changes.

We and our genes are much more flexible than we have ever thought before. Various wider environmental factors, as described by Dahlgren and whitehead, interact with our genes at various stages in our

development but especially at certain high phenotypic plasticity times, i.e. prenatal and post natal period, early childhood and at pre-puberty, leading to phenotypic changes and various disease states. Not only our genetic and epigenetics inheritance influence our ability at education, attaining good socioeconomic status and living conditions, but the environment that surrounds us interact with our genes influencing health outcomes of our children and grandchildren. So these gene-environment arrows of influence go in both directions.



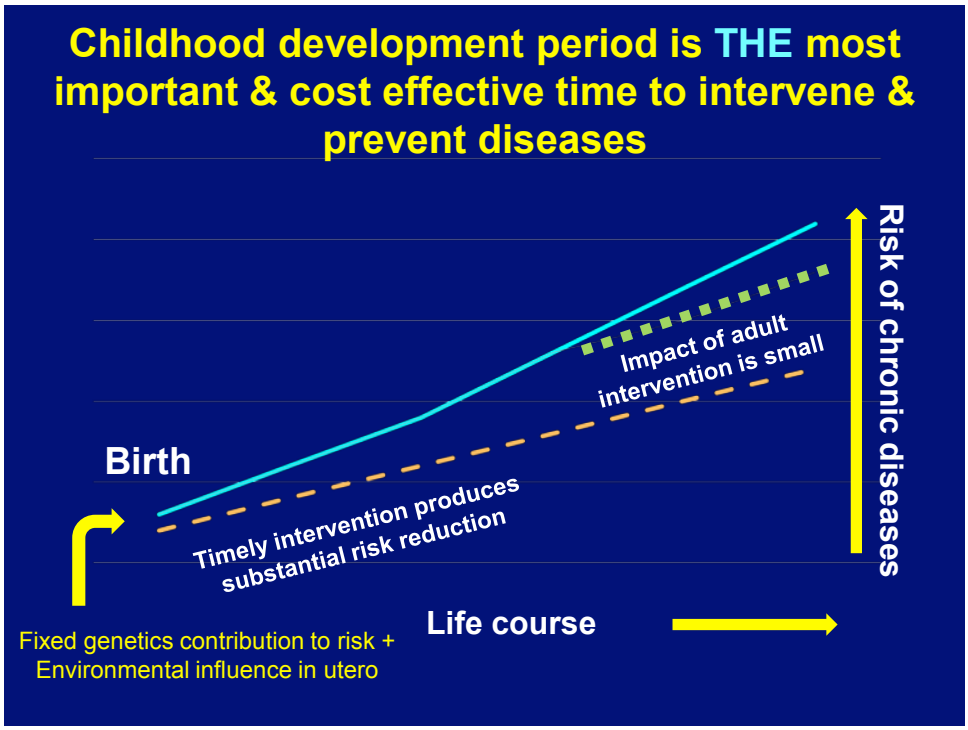
Evidence has been mounting over several decades but more strikingly from genomics research in the last decade about the importance of gene-environment interactions especially in pregnancy and childhood. Knowledge about how the wider environmental factors are 'turning the genes on and off', the new science of epigenetics, is gaining a wider coverage and influence. Evidence in mammals is showing that these gene switches (changes or markers) can be passed on to multiple future generations when they affect pregnant mothers and siblings at pre-puberty and they can also be reversed. The reversibility of these gene markers gives health prevention a new and reinforced emphasis but no more so than in pregnancy and childhood in humans.

Many surveys and epidemiological studies including the Marmot review and those of foetal programming of the 80s should be sufficient to justify prioritising maternity and childhood as a policy direction. Adding the epigenetics scientific findings of the last decade to the evidence's list make an urgent case for a concerted action. The urgency required is based on the latest eigenetics research findings that point towards environmental factors reinforcing genetic changes that perpetuate disadvantage in

communities for decades to come. The disadvantaged health status we encounter today in our most deprived communities and their wider environmental exposures as they stand today have already impacted several of their future generations. We have to break this cycle and break it urgently. Numerous experimental studies building up the epigenetics evidence in plants and in mammals as well as those in humans based on numerous observational and some cohort and longitudinal studies are starting to show the same findings of animal studies, and they all merit serious considerations.

The findings tell us that:

1. The health of adolescents and young people, who are the future parents, is very important for the health outcome of their future pregnancies and children.
2. The health of mothers during pregnancy is hugely important, not only for her own future health and the health of her foetus and his future health as a child and as an adult but also for the future health of her grandchildren through the effect on the germ lines forming future gametes of her developing foetus which are being formed while still a foetus in the womb.



3. The health of growing children especially in early childhood and pre-puberty is of paramount importance for the child and as he/she become an adult and for his/her children. It is the epigenetics flexibility that underlie the phenotypic plasticity period when the body is very susceptible to outside environmental factors in their widest sense (economic, psychosocial, nutritional,

environment, education and hazardous substances) at these crucial times when the gametes of the next generations continue to develop and mature.

4. There are strong experimental and observational studies found in plants, mammals and in humans and total scientific agreement that support the above three statements.

5. Transgenerational experimental research findings in animals, and observational and cohort studies in humans suggest that the impact is more than just three generations (the pregnant woman herself, her foetus and her future grand children) but several further generations down the line. There are disagreements among scientists as to whether epigenetics mechanism is the basis of this phenomenon but suggesting another genetics mechanism. The majority accept that it does happen but may disagree as to how often it does happen and how it happens.

6. The good news is although we cannot change our genes, we can change our epigenome through life style changes and concerted public health actions. Looking at it from a health economic angle, argument can be made that a health preventive action that will impact several generations (at least three) simultaneously will lead to huge savings when compared with an action on an adult in his/her post reproductive age although both can undo some of these environmental epigenetics changes.

7. Epigenetics science shows for the first time how important public health actions are to undo the wider environmental damaging changes to our health and to also tailor made public health initiatives to combat or prevent specific health problems. This science is strengthening the value of public health contributions to health of the nation.

6 What are the implications to public policy development in Wales?

There have been various initiatives aimed at improving maternity and child health, the latest one 'Building a Brighter Future: Early Years and Childcare Plan, 2013'. It shows Welsh Government intentions for the following 3 years. Scientific evidence listed in this report requires a more urgent and a stronger coordinated response but most of all a new approach to change the attitude of the whole society including the government towards prioritising children.

We also know that health of children directly influences children's educational attainment and that education also directly influence future health outcomes based on evidence summary of which are listed in

Appendix 1. A cultural shift in our society mediated through an integrated approach by governments, organisations, society and families is required whereby we prioritise 'our insurance policy' for better future by prioritising our children.

6.1 A stronger emphasis is required to prioritise all children not only in their early years. Maternal and child health programmes have to be annually accepted as number one priority and should never be on any disinvestment list unless such programmes are shown to be ineffective.

6.2 To develop health improvement programmes in antenatal clinics, in nurseries, preschool child care facilities and in schools based on a new vision guided by **the principle of 'Synergy of Combining Actions on Children's Health and Education'**. Public services like health and education have easy access to the 'theatres for actions' (antenatal services, nurseries and schools), as well as having the captive audience (mothers, babies, toddlers and school children) will facilitates the implementation of the new strategy. The combined actions on health intertwined with actions on education will act and deliver 'synergistically' where by the outcome will be more than the sum of health plus education as one strengthens and magnifies the other.

6.3 This requires a very close working arrangement between various departments in WG, NHS, LEAs and other public sectors organisations as well as voluntary, and private sectors to influence change.

6.4 The health improvement messages to the population will have to be modified taking into consideration epigenetics science findings. This includes reminding teenagers and young people to look after their body and their health as they are the guardians of our genome, and as it concerns the legacy they want to leave to their children and grandchildren. It also includes reminding pregnant women that they are the incubators of future generations not just their babies, but their babies' babies.

6.5 To advocate for enshrining the prioritisation of children in law. This could be achieved through extending the powers of the United Nations Convention on the Rights of the Child (UNCRC) that was adopted by WG in 2009 as the basis of all their policy making for children and young people. The extension should include a statement of intent to place **Children's health, education and wellbeing, from conception until after puberty, as the first priority for public policy to sustain future generations in Wales.**

Such a change in UNCRC will complement and strengthens other Welsh Assembly Laws and measures. The legislation would also include a subsidiary legal framework placing the onus upon such bodies to actively demonstrate discharge of the new legal obligation through a transparent reporting mechanism and other levers. Or this could be achieved by enshrining it within the Well-being of Future Generations (Wales) Act 2015.

Based on the fact that the NHS is the only statutory body in contact with all mothers and children, and the leading role that local government plays in education and other services, extending UNCRC should:

- Place a duty on the Welsh Government to prepare a Children Plan every four years, setting out how it will prioritise children and how it aims to ensure every child has the chance to grow up fit and healthy, achieving school ready status, and better health and educational outcomes at all childhood stages (0-18 years) which would:
  - Ensure total government departmental coordination of children's health, education and social care.
  - Ensure that prioritising children becomes the mainstay and the foundation upon which, a consistant sustainable total systems improvement programmes are built.
  - Children should be number one priority on any organisation's investment list and should never be on any disinvestment list unless the particular programme was found to be ineffective.
  - Raising the standards of training programmes, recruitment, selection and admission requirements for training programmes for all professionals dealing with health, social care and education of children.
  - Identify and report by local area on all aspects of poor health
  - Identify the responsibilities of different agencies to tackle them
  - Propose actions to target the most deprived communities and reduce the gap in outcomes.
  - Place a joint duty on local health boards and local authorities to prepare child health improvement and health equality plans every four years, setting out how with others they will act.

This should require them to set out how they would:

- Identify differences in health status in different communities
- Design and implement a programme to improve outcomes
- Target the most deprived communities and reduce the gap in outcomes

- Report annually on progress.

- Place a duty on Public Health Wales to advise the responsible bodies on effective interventions to discharge their duty.

- Place a duty on the Wales Audit Office to monitor progress, especially through reviewing the plans.

6.6 Why seeking the prioritisation of children to be enshrined in law?

Only by enshrining prioritising children as a policy in a Bill will fully achieve our aims in improving the nation's health and future prosperity of this country because,

- It shows that strong convincing evidence have been sought and found.
- Legislations will ensure wide coverage of this important area and give it the gravitas it deserves. It shows that the country as a whole is committed and in public to achieve that good cause.
- It obliges ministers, organisations, groups and individuals to give it its rightful place.
- It will raise the society's awareness, changing the culture and attitudes which are pre-requisite of any big societal change that is required to give children their rightful place in society and be valued and cherished as the country's insurance policy for the health and prosperity of future generations.
- It will strengthen other child laws and circumvent the need to have a new law banning the smacking of children as children's prioritisation law will encompass that and go beyond that important principle.
- A bill that follow the example of Scandinavian countries in being broad in nature that create conditions for children's health and well being to be at the forefront of policies in every governmental department and every public, private and voluntary organisation will eventually lead to a reduction in inequalities in health in Wales.

6.7 Prioritisation and emphasis on improving health and developmental and educational needs of mothers and children means

- We have to raise the bar by which the quality of health and educational systems for children are assessed. Raising the threshold of what is considered as acceptable standards of education, health and social care for children.

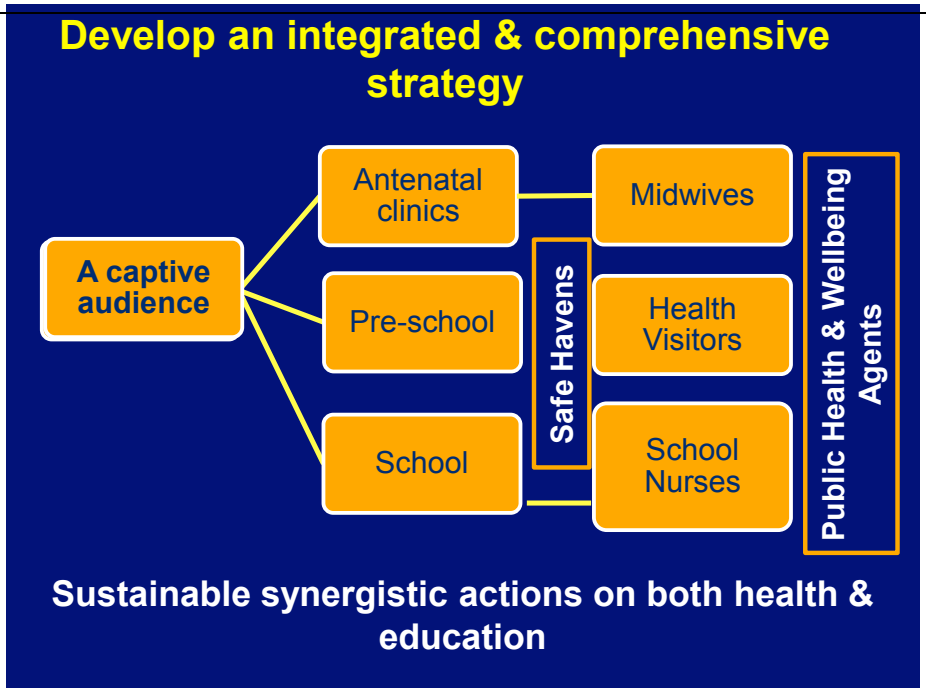
- Raising the bar means standards of selection for professional education and development of midwives, health visitors, school nurses and community nurses as well as children nursery nurses, school teachers and head teachers have to be raised. As a society we are going to value our children so much that we want the best caliber of staff to look after them and after their needs and their education. This means we

  select the best caliber of people, train them the best, respect and value them the best and remunerate them better than thus far. School nurses, health visitors and midwives training programmes should adapt towards creating a new cadre of transformed professionals acting like public health and well being agents for mothers and children of all ages.

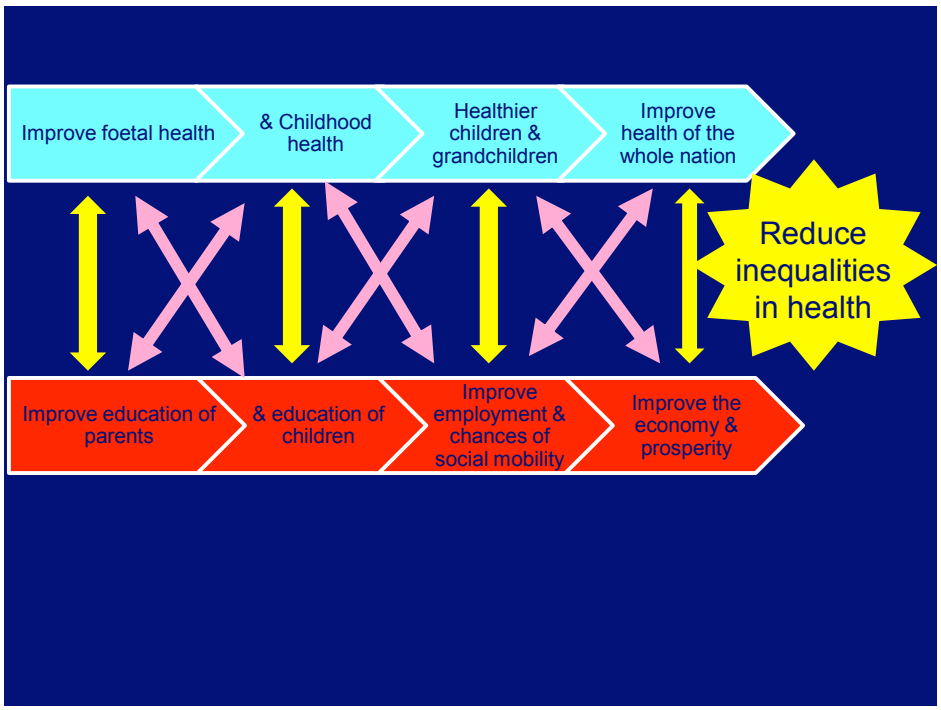
- It has ramification on the quality of accommodations of nurseries and schools, playing fields and other child facilities.

- It also has ramifications on the cost, taxes, quality, availability and affordability of children's food and commodities.

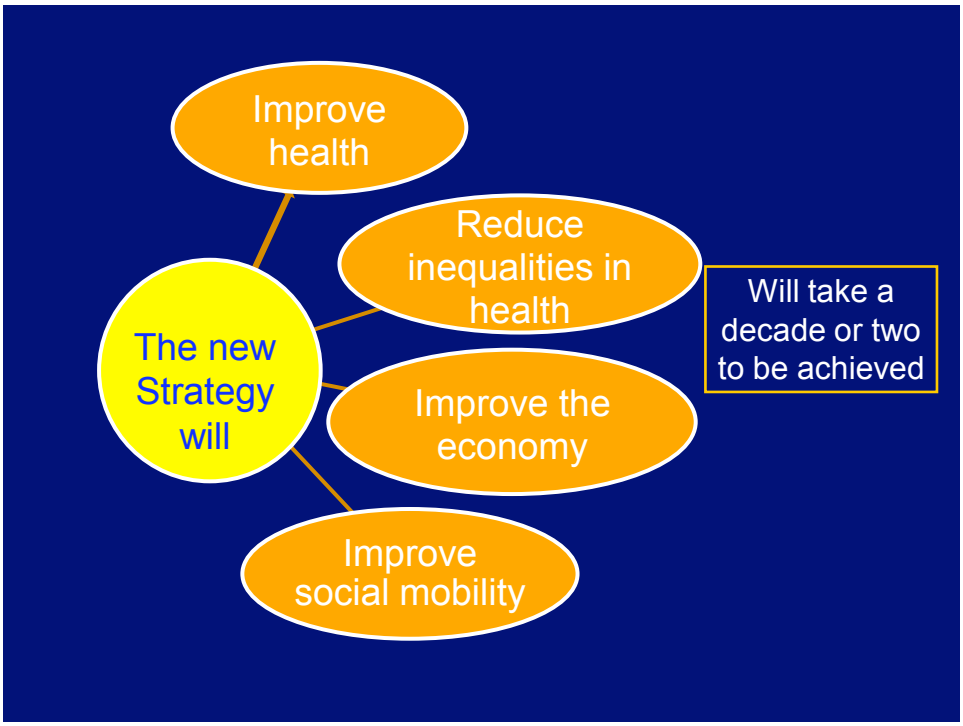
- Working effectively towards transforming antenatal clinics, nurseries and schools into 'safe havens' for all children, especially those from poorer background. Nurturing every child whatever their ability to achieve their potential should be further emphasised.



6.7.1 Government policies on children's health and education have to be the centre stage of government priorities for many years. Only a consistent approach will ensure healthier future generations and a society which has less inequality in health and has a better economic prospect as the standards of both health and education consistently rise.



6.7.2 It has implications to other policies and employment laws concerning maternity, child care and child protection as it reinforce their values. Future policies in these areas must reflect the new knowledge that considers pregnancy as an incubator for future generations.



7 What are the implications to the wider society in Wales

7.1 The way we treat and view ourselves would have to adapt to the new concept that urge us to consider ourselves as 'the guardians of our genome'.

7.2 Putting children first in family, groups, communities and the society at large will with time be accepted as the normal attitude by all.

7.3 Such attitudes will create ripple effects on other attitudes such as those towards older and infirm people or those vulnerable in society. It may well have a negative impact on self centeredness and selfishness within families and in the society at large, for example on the divorce rate.

7.4 We should educate the public of the importance of mitigating the detrimental influence of some adverse environmental

factors and adopting healthier lifestyles to combat these influences and undo some of this damage. We cannot change our genome but we can change our epigenome. Informing the public and encouraging new learning about the importance of epigenetics, i.e. the environmental influence on our genes, will help to accept and increase the value public health advice.

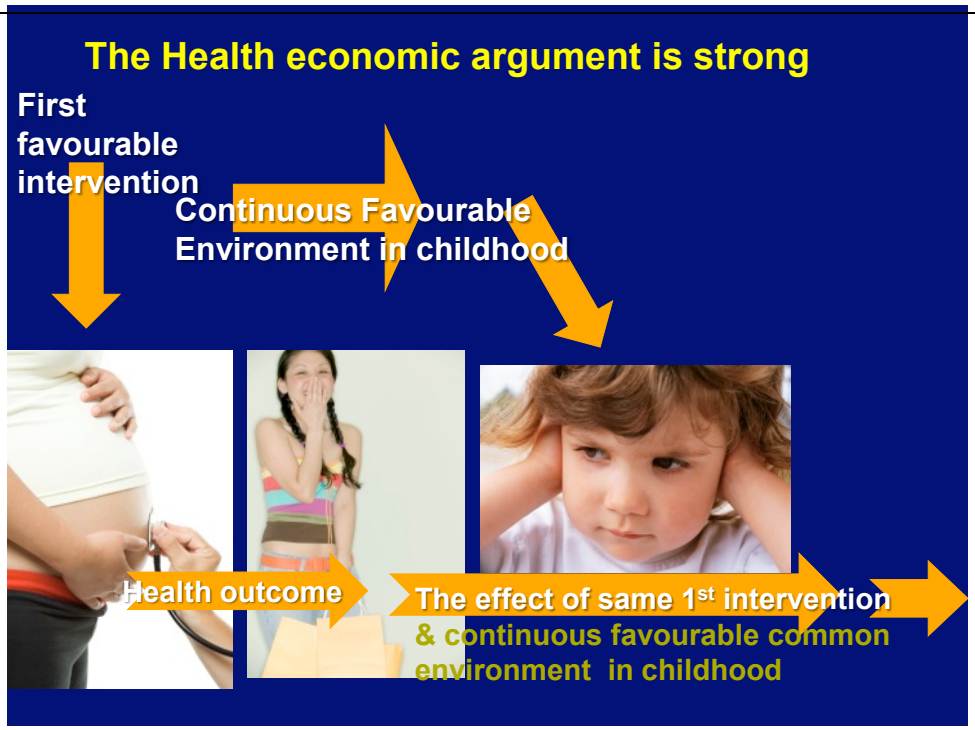
8 What are the health economic implications of a new strategy shaped by epigenetics research?

8.1 Any future business case for investment in prevention and health improvement should include the health economics case for epigenetics.

8.2 The importance of public health actions in reversing the wider environmental influence on our genome and consequently on our health should increase their health economic evaluation.

8.3 Prevention of long list of chronic and serious diseases by providing effective public health programmes for the population including adopting healthier life style has never been more valuable as confirmed and promoted by epigenetics science. The cost of these preventive programmes will be dwarfed by the benefits reaped through preventing the impact of ill health on our services over the life course and over several generations.

8.4 Looking at it from a health economic angle, argument can be made that a health preventive action in pregnancy or childhood that will impact several generations (at least three) simultaneously will lead to huge savings when compared with an action on an adult although both can undo a lot of these environmental epigenetics changes. Thus the argument to prioritise maternity and childhood is made.



Conclusion

We continue to trail back behind every other rich nation, including other UK countries, at every parameter from indices of health, education and wellbeing of children to the inequalities in health gap between rich and poor which continues to widen. Reading this report some may argue that

a. The main message of the importance of children as a policy direction is not new

b. That they have already been doing it as they start counting projects and policies they have produced

So what's new this report is bringing?

1. What we do or fail to do now as families, community, society and government will not only affect this generation but several future generations.

2. This realisation necessitate urgency in action

3. We need to accept as a society that our insurance policy for a better and sustained Wales is to give our children the priority in everything we do.

4. The change in attitudes and all that is required necessitate a fundamentally new approach of demanding the best quality systems, best cadre of staff and policy makers who deal with health and education of children

5. What is required is so fundamental to future survival and prosperity of this country that necessitates enshrining children's priority in law.

Appendix 1 - The evidence

(As of August 2015)

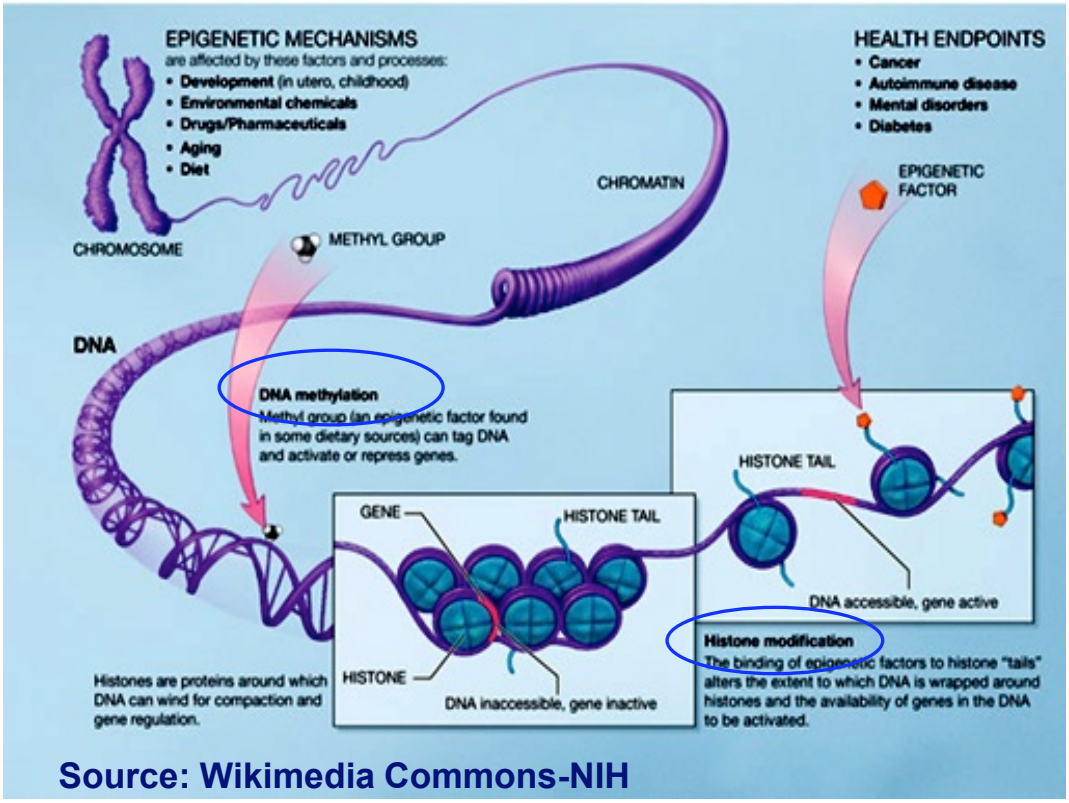
What is the evidence from epigenetics research?

Epigenetics refers to the regulation of gene expression by the chemical modification of DNA, or of the histone proteins on which DNA is usually wrapped, or microRNA changes. This modification is either the addition of methyl groups (a carbon atom and three hydrogens) to the DNA or of acetyl groups (two carbons, three hydrogens and an oxygen) to the histones. Methylation switches genes off, while acetylation switches them on.

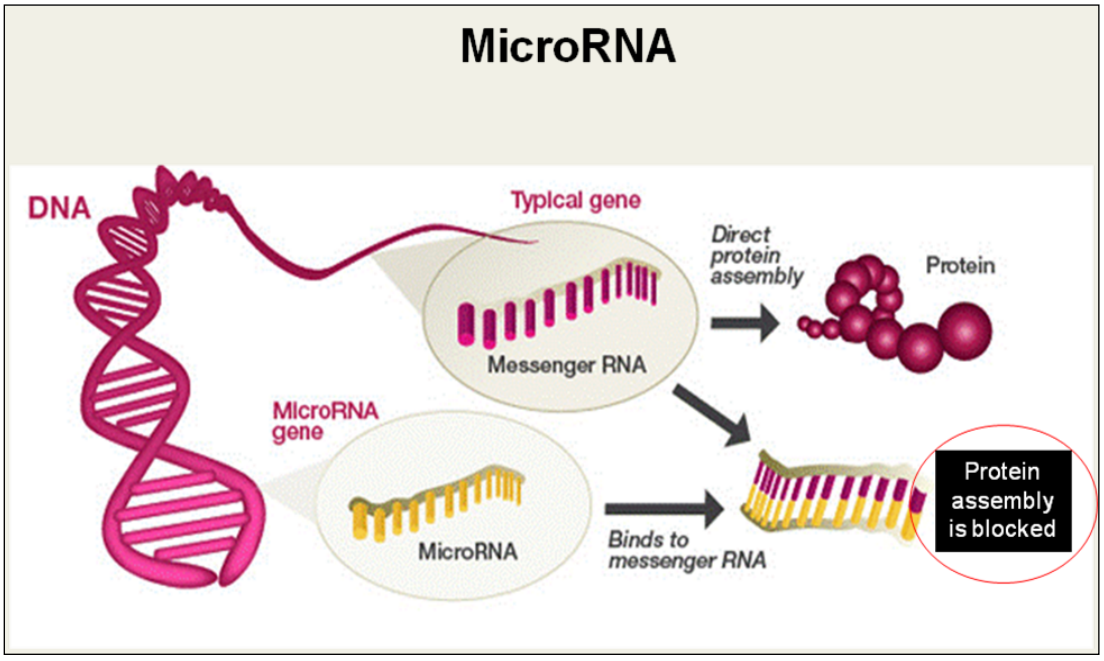
History of epigenetics

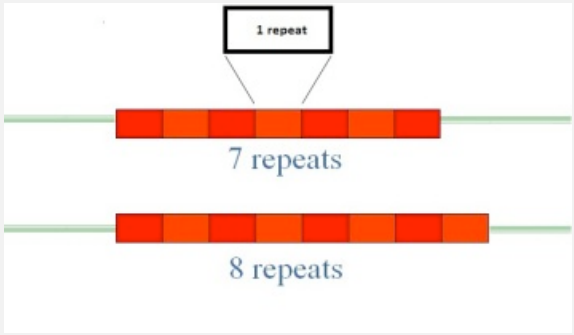
Dana C. Dolinoy and Christopher Faulk reviewed the history of epigenetics. The term they wrote "epigenetics" was popularised in the early 1940s by developmental biologist Conrad Waddington (1940) to explain "the interactions of genes with their environment, which bring the phenotype into being." In the 1970s[16],[17] first proposed covalent chemical DNA modifications, including methylation of cytosine-guanine (CpG) dinucleotides. The revelations several decades later that X inactivation in mammals and genomic imprinting are regulated by complex and multifactorial mechanisms[18] resulted in an updated definition, describing **epigenetics as heritable changes in gene expression that occur without a change in DNA sequence**, including the modification of DNA methylation and chromatin remodeling[19]. The genomics revolution inspired the investigation of genome-wide rather than local gene analyses, and the term "epigenomics" was coined as the study of the "effects of chromatin structure including the higher order of chromatin folding and attachment to the nuclear matrix, packaging of DNA around nucleosomes, covalent modifications of histone tails (acetylation, methylation, phosphorylation, ubiquitination), and DNA methylation[20]".Finally, evidence that demonstrated the resistance of certain gene loci to methylation reprogramming during embryogenesis revealed that epigenetic modifications can be inherited not only mitotically but also transgenerationally[21,22,23].

Changes in the epigenome induced by the environment have been documented in diverse animal phyla, ranging from insects to rodents to humans. These include chromatin remodeling, histone tail modifications, and DNA methylation, and more recently the list has expanded to encompass non-coding RNA and microRNA gene regulation[24]. Other mechanisms that are being elucidated include: involvement of DNA repeats; transposable elements and jumping genes and bacteriom affecting chromatin structure and transcription.

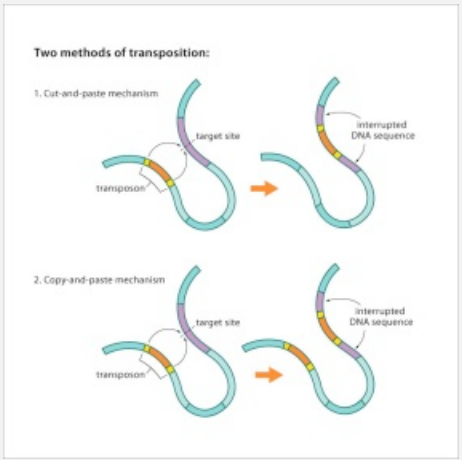


Source: Wikimedia Commons-NIH





Repetitive regions of non-coding DNA are conserved within a person's DNA, & they are passed from parents to offspring in a Mendelian way, like genes.



Transposon is a small piece of DNA that inserts itself into another place in the genome 'Jumping Genes'

Epigenetic factors (also known as epigenetic marks) control many of the normal functions of cells in our bodies[1]. For example, epigenetic marks control how and when certain genes are turned on and off to help the body grows and develops into various tissues forming different organs at embryological developement[2]. Even those epigenetic changes that are inherited seem to be subsequently reversible.

Sometimes, epigenetic marks cause certain genes to be turned on or off at different stages of the body's growth and development in a way that leads to diseases. For example, certain genes normally work to protect against cancer. Some epigenetic marks can turn these genes off, increasing the risk of cancer. Scientists still do not fully understand and still unraveling why certain epigenetic marks switch off the genes we need to stay healthy, or turn on genes that lead to disease[3].

There are accumulating evidences, both from mammals and insects, points towards an emerging role for DNA methylation in the regulation of phenotypic plasticity.

Examples of epigenetics phenomena in animals *include* ***the bees'*** *development. The royal diet, the royal jelly is a complex, protein-rich substance secreted from glands on the heads of worker bees. A larva destined to become a queen is fed large quantities of royal jelly inside a specially constructed compartment called a queen cup.*

The larvae that develop into workers and queens are genetically identical. But as a result of the royal jelly diet, the queen will develop functional ovaries and a larger abdomen for egg laying, while worker bees remain sterile. She'll also develop the necessary behaviours to act as queen, such as killing rival queens, making communication sounds known as "piping," and going on "mating flights." The queen is fed royal honey exclusively for the rest of her life. Scientists have determined that royal jelly silences a key gene (Dnmt3), which codes for an enzyme involved in genome-wide gene silencing. When Dnmt3 is active in bee larvae, the queen genes are epigenetically silenced and the larvae develop into the default "worker" variety. But when royal jelly turns Dnmt3 off, certain genes jump into action that turn the lucky larvae into queens.

Another example is the ***desert locust****. Locusts are the swarming phase of certain species of short-horned grasshoppers in the family Acrididae. These are species that can breed rapidly under suitable conditions and subsequently become gregarious and migratory when their populations become dense enough. Genetically identical locusts exhibit two phases 'solitary' and 'gregarious' determined by their environment, the latter will form the locust swarms that have annually devastated acres of farm land in many parts of the worlds.*

The gregarious and solitary locust phase animals differ not only in their physical appearance (e.g., colour and size), but also in their behavioural and physiological traits. Recent studies demonstrate differences in visual abilities between the phases that match the needs of each phase (e.g., the ability to see looming objects)[25]*. While an adult animal cannot change its physical form, the root of the epigenetic change can occur within a few days; for example, when exposing a solitary female to crowding conditions she will begin to lay gregarious eggs within a few days. Solitary locusts have more sensitive hearing. Understanding differences in the hearing capabilities of different phases of locusts has many implications. First of all, it is an example of how the environment can influence traits to be best suited for the animal's needs. In this instance, solitary animals exhibit greater sensitivity perhaps to better perceive predators as they are not protected by living amongst others in a group. Alternatively, a greater hearing ability may be used for mate location over larger distances. Hearing has evolved at least seven times within insects so understanding the differences in the ears may also lead to evolutionary as well as mechanistic discoveries.* Schistocerca gregaria*, also produces more offspring of the gregarious swarming phenotype when breeding in crowded conditions and this is how they increase the size and the waves of locust swarms*[26]*.*

Many diseases are caused by a combination of different types of changes in many different genes. Some of these changes are genetic mutations in the DNA that are passed along in families. Some are mutations that happen randomly or because of environmental factors. And some are epigenetic changes caused by environmental or other factors.

Many diseases and conditions are linked to epigenetic or developmental epigenetic changes. So far, scientists have been able to link the following diseases to epigenetics[1,4,5]:

- Obesity
- Heart disease
- Various cancers
- Autism
- Some rare genetic/epigenetics disorders such as Fragile X syndrome, ATR-X syndrome, an intellectual disability, Angelman syndrome, Prader-Willi syndrome, Beckwith Wiedemann syndrome, a congenital growth disorder, Rett syndrome, Rubinstein-Taybi syndrome, a rare intellectual and developmental disorder and Coffin-Lowry syndrome.
- The above list have increased in recent years to include neurodegenerative disorders, bipolar disorder, schizophrenia, atherosclerosis, hypertension, SLE, kidney diseases, asthma and insulin resistance.

Smoking, child abuse and socio-economic position

In the **1958 British Birth Cohort study** blood from forty 45-year old males participating, chosen from Socio Economic Position (SEP) extremes were analysed. The DNA found to carry distinct DNA methylation patterns associated with child socio-economic position[27], prenatal tobacco exposure and child abuse[28]. The methylation signature of early-life SEP in adult blood DNA taken at 45 years is consistent with epigenetic mechanisms contributing to the association between early-life SEP and adult health.

Understanding how and when environmental exposures affect gene regulation may provide insights into ways to prevent disease by reducing exposures early in life, instead of treating the disease when symptoms occur in adulthood.

Studies of hippocampus from suicide victims who had known histories of childhood abuse showed higher methylation when compared with those who were not abused[29]. These findings translate previous results from rat to humans and suggest a common effect of parental care on the epigenetic regulation of hippocampal glucocorticoid receptor expression.

Diet, obesity, exercise and diabetes

Another international study has found **an association between lower consumption of carbohydrates during early pregnancy and the activity of a gene thought to be linked to increased fat levels in children.** A research team from the University of Southampton found that mother's diet during pregnancy may influence the risk of obesity in her child in later life[30]. They found that epigenetic changes in the DNA of children at birth allowed researchers to predict their body weight later on in childhood. Women were asked to fill in a food questionnaire during

pregnancy. Their children's fat levels were measured at either age 6 and 9. The findings were then compared with DNA extracted from the children's umbilical cord blood. The study found associations between eating low levels of carbohydrates during the early stages of pregnancy and epigenetic changes in the child's DNA, which are in turn associated with a heavier weight.

Studies in animals have already shown that diet during pregnancy can be linked to epigenetic changes in DNA. However, this is the first time such a link has been seen in humans. Susceptibility to obesity cannot simply be attributed to the combination of our genes and our lifestyle, but can be triggered by influences on a baby's development in the womb, including what the mother ate. It explains 25% of the difference in the fatness. The effect was found to be considerably greater than birth weight and did not depend on how thin or fat the mother was. The finding strengthens the case for all women of reproductive age having greater access to nutritional, education and lifestyle support to improve the health of the next generation, and to reduce the risk of the conditions such as diabetes and heart disease, which often follow obesity.

Another study had revealed that the **patterns of epigenetic modifications in monozygotic twin pairs diverge as they become older**. Differences in epigenetic patterns in genetically identical individuals could be explained by the influence of both external and internal factors[31]. Smoking habits, physical activity, or diet, among others, are external factors that have been proposed to have a long-term influence on epigenetic modifications. By using whole-genome and locus-specific approaches, researchers found that approximately one-third of MZ twins harbored epigenetic differences in DNA methylation and histone modification.

A lot of research has also been done to **elucidate the complex etiologies of both obesity and type II diabetes (T2D)**. And although many genetic risk loci have been identified these do not completely explain the disease onset. Researchers have turned their attention to the considerable epigenetic component of obesity and type 2 Diabetes development. For many years, the most effective preventative treatment suggested for both obesity and T2D is exercise and a healthy diet. Research has now shown that exercise alone is sufficient to change our epigenome and possibly our destiny. A recent study published in PLOS Genetics evaluated genome-wide methylation in adipose tissue in healthy men with and without a family history of T2D[32]. This fatty tissue is metabolically important and plays a role in total glucose equilibrium. These men were typical coach potatoes with an average weight of 91.8±11 kg and a BMI of 28.2±2.9. They were asked to participate in a one-hour spin session, and two one-hour sessions of aerobics a week, without changing their diet or daily activity for six months. The average participation was 1.8 sessions per week. As well as a decrease in waist-hip ratio, which was also associated with increased methylation of a gene previously associated with waist-hip ratio[33], significant methylation

changes were observed in 18 candidate genes previously associated with obesity and 21 genes associated with T2D. Laboratory experiments with some of these genes showed that changes in methylation also changed gene expression, which in turn can play an important role in disease pathogenicity.

This study highlights the **importance of exercise in improving overall health**. Doing as little as two hours of aerobics a week will not only improve your fitness; it can also decrease the risk of obesity and T2D. Although epigenetics in adipose tissue might only be one small part of a very complex puzzle that makes up obesity and T2D, this study provides the first detailed methylome of human adipose tissue, and possible future treatment targets for T2D and obesity. For example, one group reported that pre-diabetic mice have different epigenetic tag patterns in their sperm and that their offspring have a higher chance of developing diabetes[34]. A flurry of other biomedical and epidemiological research has strongly hinted that a susceptibility to obesity, diabetes, and heart disease can be passed on through epigenetic tags.

Both mice and human have the agouti gene, when it is completely unmethylated the mouse has yellow coat colour, is obese and prone to diabetes and cancer. When the agouti gene is methylated (as in normal mice) the coat colour is brown and the mouse has a low disease risk. Fat yellow mice and brown skinny mice are genetically identical. When researchers fed pregnant yellow mice a methyl rich diet, most of the resulting pups were brown and healthy and stayed that way for life.

More recently researchers have also found that **the age of DNA methylation of blood predicts all-cause mortality in later life[35].**

Epidemiological studies have identified numerous measures from across the human life-course that are associated with an increased risk of mortality. These include health factors such as cardiovascular disease, diabetes and hypertension, genetic factors such as presence of the *APOE* e4 allele, lifestyle variables such as smoking and education, behavioural traits such as cognitive ability, the personality trait of conscientiousness, and candidate biomarkers of age such as telomere length. In this paper researchers reported that an epigenetic biomarker (DNA methylation) was predictive of human mortality, after accounting for known risk factors. They found that two heritable DNA methylation-based measures of the difference between epigenetic age and chronological age are significant predictors of mortality in their meta-analysis of four independent cohorts of older people. Individual genetic or environmental exposures that drive the associations are not yet known, but they appear not to be clearly linked to classic life-course risk factors. The difference between DNA methylation age and chronological age predicts mortality risk over and above a combination of smoking, education, childhood IQ, social class, *APOE* genotype, cardiovascular disease, high blood pressure, and diabetes. It may therefore be possible to think of DNA methylation predicted age as an 'epigenetic clock' that measures biological age and

runs alongside, but not always in parallel with chronological age, and may inform life expectancy predictions. Their results imply that epigenetic marks, such as gene methylation, are like other complex traits: influenced by both genetic and environmental factors and associated with major health related outcomes.

Transgenerational epigenetic observations and inheritance in mammals

The phenomenon is nicely illustrated on University of Utah Genetics Science Learning Centre Website. We used to think that a new embryo's epigenome was completely erased and rebuilt from scratch. But this isn't completely true. Some epigenetic tags remain in place as genetic information passes from generation to generation, a process called epigenetic inheritance.

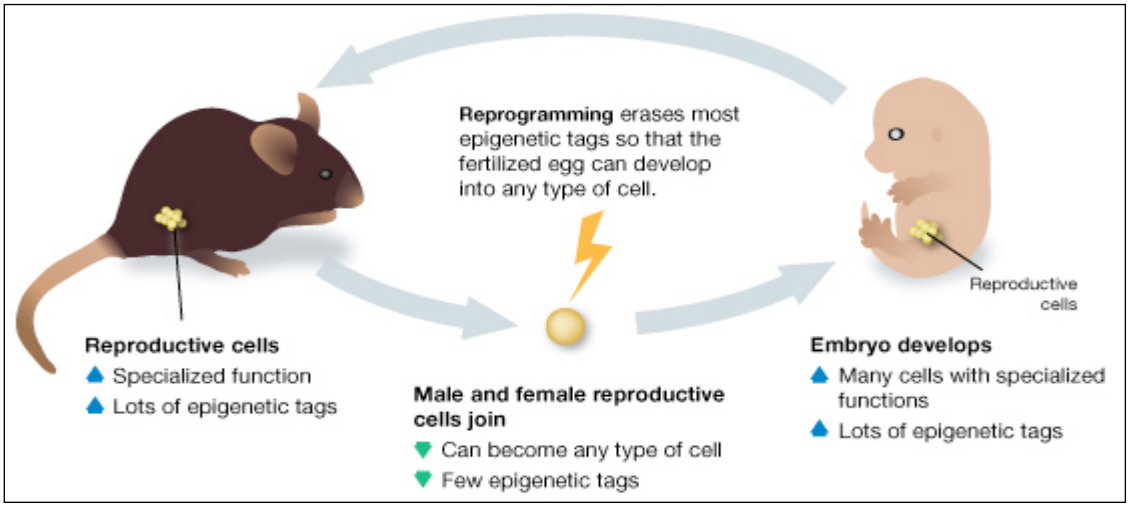
Epigenetic inheritance is an unconventional finding in recent years. It goes against the idea that inheritance happens only through the DNA code that passes from parent to offspring. It means that a parent's experiences, in the form of epigenetic tags, can be passed down to future generations.

As unconventional as it may be, there is little doubt that epigenetic inheritance is real. In fact, it explains some strange patterns of inheritance geneticists have been puzzling over for decades.

Most complex organisms develop from specialized reproductive cells (eggs and sperm in animals). Two reproductive cells meet, then they grow and divide to form every type of cell in the adult organism. In order for this process to occur, the epigenome must be erased through a process called "reprogramming."

Reprogramming is important because eggs and sperm develop from specialized cells with stable gene expression profiles. In other words, their genetic information is marked with epigenetic tags. Before the new organism can grow into a healthy embryo, the epigenetic tags must be erased.

At certain times during development (the timing varies among species), specialized cellular machinery scours the genome and erases its epigenetic tags in order to return the cells to a genetic "blank slate." Yet, for a small minority of genes, epigenetic tags make it through this process and pass unchanged from parent to offspring.



Source: University of Utah Genetics Science Learning Centre Website

Reprogramming resets the epigenome of the early embryo so that it can form every type of cell in the body. In order to pass to the next generation, epigenetic tags must avoid being erased during reprogramming[36].

The Challenges of Proving Epigenetic Inheritance

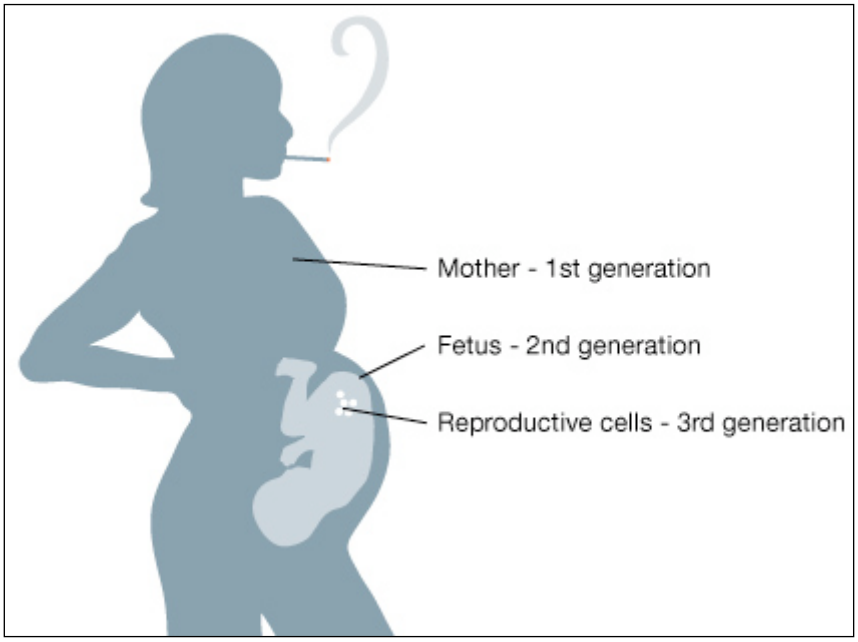
Proving epigenetic inheritance is not always straightforward. To provide a watertight case for epigenetic inheritance, researchers must:

- **Rule out the possibility of genetic changes**

  In organisms with larger genomes, a single mutation can hide like a needle in a haystack.

- **Show that the epigenetic effect can pass through enough generations to rule out the possibility of direct exposure**
  In a pregnant mother three generations are directly exposed to the same environmental conditions at the same time. An epigenetic effect that continues into the 4th generation could be inherited and not due to direct exposure.

Researchers face the added challenge that epigenetic changes are transient by nature. That is, the epigenome changes more rapidly than the relatively fixed DNA code. An epigenetic change that was triggered by environmental conditions may be reversed when environmental conditions change again.



Source: University of Utah Genetics Science Learning Centre Website

Three generations at once are exposed to the same environmental conditions (diet, toxins, hormones, etc.). In order to provide a convincing case for epigenetic inheritance, an epigenetic change must be observed in the 4th generation[37].

Biologists first observed this 'transgenerational epigenetic inheritance' or some scientists call it epigenetics transgenerational responses, in plants. Tomatoes, for example, pass along chemical markings that control an important ripening gene[38] [2] and in rice's resistance to infection which was stably inherited over nine generations[39]. But, over the past few years, evidence has been accumulating that the phenomenon occurs in rodents and humans as well.

Epigenetic inheritance has been demonstrated in plants and worms. Mammals go through two rounds of epigenetic "reprogramming" -- once after fertilization and again during the formation of gametes (sex cells) -- in which most of the chemical tags are wiped clean.

There are a lot of studies that suggest that transgenerational epigenetic inheritance via the gametes can occur, but there is a dearth of studies that have rigorously established the molecule that is involved in the transfer of information from one generation to the next. Molecular biologists studying transgenerational epigenetic inheritance via the gametes have generally focused on the nucleus. However, recent studies suggest that *trans*-acting and/or non-nuclear factors could be involved. For example, RNA, which occurs inside and outside the nucleus. So possible mechanisms may involve epigenetic marks: that is, DNA methylation and histone modifications. Scientists have also considered RNA and *trans* effects. An emerging theme in cases of transgenerational epigenetic inheritance via the gametes is the involvement of repeats and

transposable elements, and recent progress in our understanding of the establishment of heterochromatin at repeats reveals the importance of RNA; this raises the possibility that RNA may have a role in transgenerational epigenetic inheritance via the gametes[40]. It is worth noting that the draft human genome sequence revealed 8% of our DNA to be retroviral in origin[41]. It is conceivable that inheritance of variable epigenetic states at few random sequences sites contributes to the phenotype of an individual.

An extreme example of epigenetic regulation is a group of genes called imprinted genes. Here, only one copy of the gene is active, depending on whether it came from mother or (in other instances) from father. The other copy is silenced by DNA methylation during sperm or egg formation.

Almost any complex disease is likely to be caused, in part, by epigenetic changes. Scientists are just now starting to uncover the specific changes that contribute to all the various diseases.

An experimental study from Emory[42] in USA found that lab rats conditioned to fear a certain smell will pass that fear on to their children. The inheritance happens biologically, even without behavioural contact. If the father runs from a certain smell, his pups will too, even if they don't know why. Mouse pups — and even the offspring's offspring — can inherit a fearful association of a certain smell with pain, even if they have not experienced the pain themselves, and without the need for genetic mutations. Children of post traumatic stress disorder sufferers, for instance, have been shown to have lower levels of stress-response hormones, possibly as a result of their parents' trauma. But these experiments could always be explained away as more nurture than nature, the behavioural effects of growing up with a traumatised parent.

A study from Washington State University showed that environmental toxins can cause inherited diseases[43]. They found that exposure to an environmental toxin during embryonic development can cause an animal, and almost all of its descendents, to develop adult-onset illnesses such as cancer and kidney disease. Their discovery suggests that toxins may have played a role in the rapid increase in localized geographic areas of diseases that were previously thought to be caused primarily by genetic mutations.

This 2012 research findings builds on the group's 2005 finding that exposure to a toxin during embryonic development can cause fertility problems in male rats that are passed to later generations. Skinner et al exposed pregnant rats to an environmental toxin during the period that the sex of their offspring was being determined. At that stage of development, the genes of the male embryo's sex cells (future sperm) are uniquely vulnerable to reprogramming. The researchers used vinclozolin, a fungicide commonly used in vineyards. Vinclozolin belongs to the class of compounds called endocrine disruptors, synthetic chemicals that interfere with the normal functioning of reproductive hormones. They used higher

levels of the toxin than are normally present in the environment, but their study raises concerns about the long-term impacts of such toxins on human and animal health, particularly in exposures during early- to mid-pregnancy (6 weeks to 5 months in humans). Further work will be needed to determine whether lower levels have similar effects. Pregnant rats that were exposed to vinclozolin produced male offspring with low sperm counts and a high incidence of adult-onset diseases. Despite their low fertility, those males were still able to produce offspring. When they were mated with females that had not been exposed to the toxins, their offspring had the same problems.

The effect persisted through four generations, with about 85 percent of the offspring in each generation developing conditions such as breast tumors, prostate disease, kidney disease, immune system abnormalities, and premature aging. Some mice came down with just one disease, but the majority suffered multiple ailments. Skinner wrote "A human analogy would be if your grandmother was exposed to an environmental toxicant during mid-gestation, you may develop a disease state even though you never had direct exposure, and you may pass it on to your great-grandchildren." The team identified 25 segments of DNA in the affected rats that had altered patterns of methyl groups compared to control rats. Their results suggest the genes controlling susceptibility to the observed diseases lie somewhere within those 25 segments. Skinner said the broad-spectrum effect of the changes, causing diseases in many organ systems, was a notable result that could provide valuable clues about how diseases develop. He wrote 'such changes might play a role in human diseases such as breast cancer and prostate disease, whose frequency is increasing faster than would be expected if they were the result of genetic mutations alone'. Scientists have long known about epigenetic changes, but their high rate of heritability and their importance in the control of gene activity were not appreciated until recently.

Skinner said the finding that an environmental toxin can permanently reprogram a heritable trait also may alter our concept of evolutionary biology. Traditional evolutionary theory maintains that the environment is primarily a backdrop on which selection takes place, and that differences between individuals arise from random mutations in the DNA. The work by Skinner and many other researchers raise the possibility that **environmental factors may play a much larger role in evolution than has been realised before**. This work is at the forefront of a paradigm shift in scientific thinking. It is changing the way the causes of disease are viewed, as well as the importance of lifestyles and environmental influence. What people do no longer just affects themselves, but can determine the health of their children and grandchildren in decades to come. The genome is continually surprising biologists with how fast and fluidly it can change gene expression — and thus phenotype.

In rats, maternal grooming behaviour effected glucocorticoid receptor expression in the brain of their offspring. High grooming mothers

produced less fearful offspring who showed better physiological stress control[44]. Epigenetic profile erased and reset de novo during gametogenesis. Nonetheless, researchers have identified element that escaped systematic DNA demethylation in mouse primordial germ cells, providing a potential mechanistic basis for transgenerational inheritance[45].

Dr.Virender Rehan of the Los Angeles Biomedical Research Institute, and his colleagues showed that **if pregnant rats are exposed to nicotine, not only will their offspring develop the asthma induced by this drug, so will the offspring of those offspring[46]**. They injected their rats with nicotine when they were six days pregnant. (Rat pregnancies last 22 days.) They then allowed them to give birth and raised the pups to the age of three weeks, before some were examined. The rest were allowed to mature and breed, and their own offspring were similarly examined. There was, however, no further administration of nicotine. The pups of the treated mothers had asthmatic lungs. The organs' airways were constricted, and molecular analysis showed abnormally high levels of fibronectin and collagen—which would stiffen the lung tissue—and also high levels of receptor molecules for nicotine. That was expected, since the developing embryos were exposed to the nicotine when their mothers were treated. However, when the team did similar tests on the grand-offspring of the treated mothers, they got similar results. Those grand-offspring had not been exposed to nicotine. Researchers argued that nicotine is not only affecting lung cells, but also affecting sex cells in ways that cause the lungs which ultimately develop from those cells to express their genes in the same abnormal ways. This suggests that epigenetics really might act like the biblical curse: that the sins of the fathers (or, in this case, the mothers) will be visited on the sons, even unto the third and fourth generations.

Transgenerational epigenetic observations and inheritance in humans

Reports of multigenerational epigenetic effects in human populations although increasing, they have been scant 65 years ago in part because phenotypic records across generations have rarely been collected and in part because ruling out genetic and environmental confounders is extremely difficult. However, a few studies have been published.

In an observational study that was conducted in Sweden utilising historical records, including harvests and food prices, in an isolated municipality, Överkalix, 303 probands born in 1890, 1905, or 1920, and their 1,818 parents and grandparents were studied. This transgenerational inheritance was observed with exposure during the slow growth period (SGP). The SGP is the time before the start of puberty, when environmental factors have a larger impact on the body. The ancestors' SGP in this study was set between the ages of 9-12 for boys and 8–10 years for girls. This occurred in the SGP of both grandparents, or during the gestation period/infant life of the grandmothers, but not during either grandparent's puberty. Females experienced a twofold higher

mortality if their paternal grandmother had good food availability during their Slow Growth Period (8-10 years old). Paternal grandfather's food supply was only linked to mortality rates of grandsons, while paternal grandmother's food supply was only linked to mortality of granddaughters. Grandsons of Overkalix boys who had overeaten died an average of 6 years earlier due to cardiovascular diseases than the grandsons of those who had endured a poor harvest. When controlled for certain socioeconomic variations, the difference in longevity increased to an astonishing 32 years! If food was plentiful, then diabetes mortality in the grandchildren increased. Women lived shorter lives on average if their paternal grandmothers experienced famine during pregnancy. A single winter of overeating as a youngster could initiate a biological chain of events that would lead one's grandchildren to die decades earlier than their peers did.

Also **observational studies of the effects of famines in Holland in the 1940s, in China in the 1950s and in the United States** over a century ago showed that they changed the lifespan and obesity rates in subsequent generations. They switched on genes that increased the accumulation of body fat in times of plenty, in order to improve survival chances in times of famine. With calorie-dense fast foods more freely available now than at any time in history, the seeds of the current obesity epidemic may thus have been sown in the 19th century. The risk of obesity can come not just from your own environment or your mother's but higher up the ancestral chain.

In the Avon Longitudinal Study of Parents and Children (ALSPAC) (Children's of the 90s) a cohort of 14,000 pregnant women in 1991-2 were followed as well as most children and fathers ever since. Fathers who smoked as pre-adolescents have increased their sons BMI at 9 years of age, but not their daughters[47]. A study looked at a range of factors that might be associated with subclinical psychotic episodes - possible warning signs of increased risk of schizophrenia in adulthood. Links were identified with impaired fetal growth[48], trauma at or around the time of birth[49], maternal smoking[50] and events in childhood itself, such as bullying[51]. An association was also found between binge drinking in mothers and behavioral problems such as hyperactivity at age four (in girls) and at age seven (in both sexes)[52]. They also identified a link between lead levels in blood at 30 months and a range of indicators at age seven to eight, including reading and writing ability, SATs results and antisocial behavior measures, even at lead levels well below the generally recognised risk level[53].

Women who suffer higher levels of stress while pregnant are more likely to have children with lower IQs and greater emotional difficulties[54,55].

Parental effects are defined as effects on the phenotype of offspring that are not determined by the offspring's genotype but instead are determined by the genotype or environmental experience of the parents.

These effects can be paternal or maternal and have been reported in a range of multicellular organisms. Such effects fit within the confines of transgenerational epigenetic effects. Some are known to involve gametic epigenetic inheritance, others are not. Some are classified as adaptive by evolutionary biologists, others are not. Adaptive parental effects are examples of soft inheritance[56].

Transgenerational inheritance of more than 3 generations in man is a totally new concept although accepted as probably happening with disagreements about the mechanisms of it, other scientists disagree about the extent and the degree. Some scientists argue that it could be due to some other 'genetics mechanisms not necessarily epigenetics such as undetected mutations in the DNA sequence, behavioural changes (which themselves can trigger epigenetic tags), alterations in the microbiome (the millions of bacteria that live in our body), or transmission of metabolites from one generation to the next. Heard and Martienssen in their Cell review article[57], have admitted that epigenetic inheritance has been demonstrated in plants and worms. But, mammals they argued are completely different. Mammals go through two rounds of epigenetic "reprogramming" -- once after fertilization and again during the formation of gametes (sex cells) -- in which most of the chemical tags are wiped clean.

They insist that characteristics many researchers assume to be the results of epigenetic inheritance are actually caused by something else (see above). It is true that environmental factors can influence epigenetic tags in children and developing fetuses *in utero*. What is far less clear, however, is whether or not these modifications truly are passed on to multiple generations. These two researchers argued that mammalian epigenetic "reprogramming" mechanisms are simply too robust.

What other non genomics evidence we already have that support the strategy change?

All childhood health parameters in Wales start from a comparatively low level. All our public health indicators showed that most of our children parameters fare badly when compared with other UK countries. Findings from PHW latest report *'Measuring inequalities: Trends in mortality and life expectancy in Wales, the Observatory 2011'* showed that the national inequality gap has widened over time (2001-2009). The gap in life expectancy has slightly widened in Wales. The gap is very wide in healthy life expectancy between the most and least deprived areas is 18.9 years for males and 17.8 years for females. This contrasts with the national inequality gap in life expectancy overall of 9.2 years for males and 7.1 years for females.

- Recent PHW report on *'Health of Children and Young People, The Observatory, 2013'* showed that 1 in 5 children live in poverty.

Almost 3 in 10 children aged 4-5 are classified as overweight or obese. 26% of those aged 16-24 reported smoking. 46% of those aged 16-24 drink above the recommended guidelines. Teenage conception rates in Wales are higher in those aged under 18 compared to England.

- The Marmot review in England 'Fair Society, Healthy Lives' report in 2010 has also shown that: "social gradient on health inequalities is reflected in the social gradient on educational attainment, employment, income, quality of neighbourhood and so on". He highlighted a real challenge to improving the health and well-being of children and young people: there is a social gradient in health, meaning the lower your social position, the poorer your health outcomes. This gradient in health outcomes is much steeper than it need be and takes effect from a very early age. Such health inequalities arise not only from family income or the quality of health services, but also from the wider social determinants of health, including: educational attainment, early childhood development and environmental factors like poor housing and a lack of access to green space. He found that People living in the poorest neighborhoods in England will on average die seven years earlier than people living in the richest neighborhoods. People living in poorer areas not only die sooner, but spend more of their lives with disability - an average total difference of 17 years.

- The second Unicef Report on *'Child well-being in rich countries, a comparative overview, 2013'* showed that the UK was in the bottom third of the league table on children's material well-being, education, family and relationships, behaviours and risks and subjective well-being and in the middle third on health and safety. The UK is in the top third on housing and the environment, middle third on all other domains except education, which remains in the bottom third. UK is 16th, which still ranks it lower in the child well-being league table than relatively poorer countries including Slovenia, Czech Republic and Portugal. Following 2007 Unicef report the Department of Children, Families and Schools published a **Children's Plan**, more resources were found for child care, schools, child health and the child poverty strategy and there was all party support for the **Child Poverty Act in 2010**. The evidence in 2013 report also pre-dates most of the policies introduced by the Government to cut the deficit. Evidence from the **Understanding Society Survey**[58] suggests that the subjective well-being of 11-15 year olds has begun to fall. Rates of young people not in education, employment and training are up and there may even be a reduction in further education rates in England.

- David Barker challenged in 1995 the idea that chronic disorders such as diabetes and cardiovascular disease are explained only by bad genes and unhealthy adult lifestyles. His *'Barker hypothesis'* proposed that the foetal environment and early infant health

permanently programme the body's metabolism and growth, and thus determine the pathologies of old age[59]. Many studies have provided evidence for the hypothesis that size at birth is related to the risk of developing disease in later life. In particular, links are well established between reduced birth weight and increased risk of coronary heart disease, diabetes, hypertension and stroke in adulthood. According to his theory, conditions in the maternal womb have a programming effect on foetal physiology, a phenomenon called *foetal programming*. It is suggested that the foetus makes physiological adaptations in response to changes in its environment to prepare itself for postnatal life. It has been found that if a foetus is deprived of adequate nutrient supply in the womb; it will be irrevocably "programmed," predisposing it to a whole host of diseases: cardiovascular disease, obesity, diabetes and cancer to name a few. Thus Barker emphasizes **developmental plasticity**, the malleable quality of life in development, as important to the aetiology of disease. Barker has further shown that there is a significant generational aspect to disease, profoundly challenging today's "lifestyle" discourse. Using data from the Helsinki cohort, a group of people born between 1934 and 1944 in Helsinki, about whom a rich amount of data was collected including their mother's height, weight, age, parity; the weight and shape of the placenta; antenatal follow-up data; and socioeconomic status, Barker has shown that a woman's lifelong nutrition significantly impacts her children's risk of disease[60].

Scientists also used the **"thrifty gene hypothesis"** proposed in 1962 by geneticist James Neel [61] to help explain why many Pima Indians are overweight. Neel's theory is based on the fact that for thousands of years populations who relied on farming, hunting and fishing for food, such as the Pima Indians, experienced alternating periods of feast and famine. Neel said that to adapt to these extreme changes in caloric needs, these people developed a thrifty gene that allowed them to store fat during times of plenty so that they would not starve during times of famine.

This gene was helpful as long as there were periods of famine. But once these populations adopted the typical Western lifestyle, with less physical activity, a high fat diet, and access to a constant supply of calories, this gene began to work against them, continuing to store calories in preparation for famine. Scientists think that the thrifty gene that once protected people from starvation might also contribute to their retaining unhealthy amounts of fat with Diabetes mellitus type 2 and metabolic syndrome caused by poor nutrition during early childhood, produces permanent effects in glucose-insulin metabolism.

- We know that improvement in education and development of children will have a major impact on social mobility and in reducing

inequalities in health. **Despite medical and social welfare advances, inequalities in childhood remain stark. The most effective time to intervene to reduce inequalities in health is in early life. Child public health is potentially the most important – and most effective - activity in health and social care, encompassing as it does interventions in health, education, housing and public policy.**

Social class remains the strongest predictor of educational achievement in the UK, where the social class gap for educational achievement is one of the most significant in the developed world. Countries with better health outcomes have less inequality in child outcomes. This is particularly true for the Scandinavian countries[62]. A key common feature in the Nordic area is the respect accorded to, and training required for, those working with children in school and early years settings. The early years case study from United Kingdom (England) showed clearly that staff qualifications had a direct impact on children's outcomes[63].

- The moral case for investing in children is compelling. In a world so rich in resources, know-how and technology, it is unacceptable that we allow today's levels of child deprivation to continue. World leaders have made commitments to children through the *UN Convention on the Rights of the Child* (UNCRC), which 192 states have ratified, and the Millennium Declaration. Investing in child-sensitive development is key to realising children's rights and meeting the *Millennium Development Goals* (MDGs). World leaders reaffirmed their commitments at the United Nations Special Session in 2002. Investing in children's well-being also has significant potential pay-offs for economic growth: greater productivity, and is crucial in breaking the cycle of intergenerational poverty. The report by World Vision International rightly calls for greater attention to health inequalities at the highest political level, prioritisation of child and maternal health in the post-2015 development agenda, and improvement of data collection[64]. Investing in adolescents means the country is better placed to reap demographic dividends as a skilled youth cohort reaches adulthood and contributes to the economy and society, and helps build social and political cohesion.

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