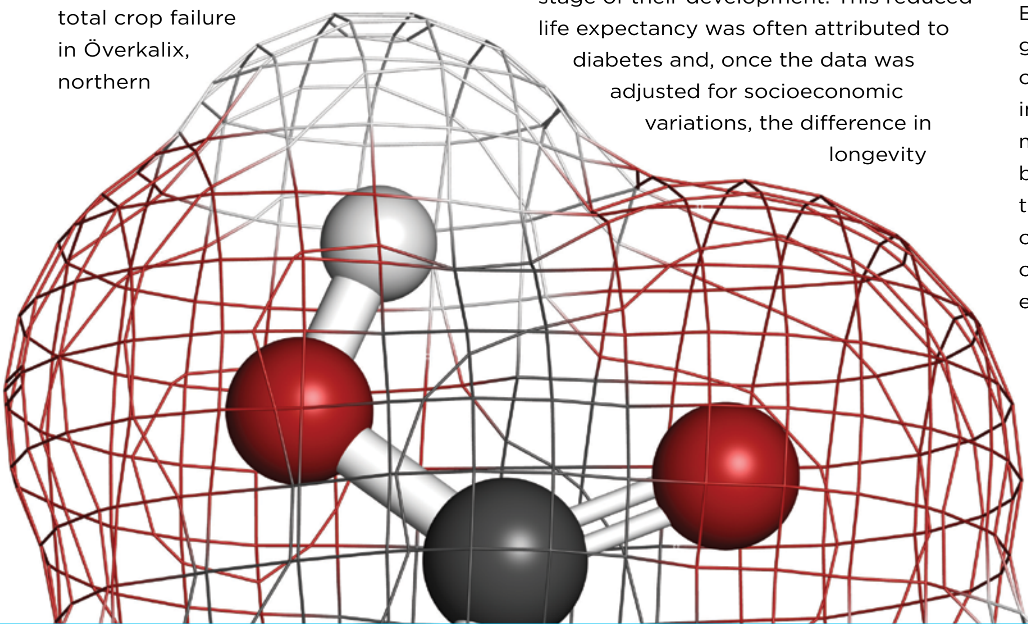
Epigenetics – adding a new layer to health

Do you feel overwhelmed with advice on what to eat and drink, or how to exercise to improve and protect your health? Pregnant women in particular are advised not to expose their developing child to alcohol, pollutants and stress. This is sound advice, since exposure at the fetal stage can have implications for generations to come. The science behind this is called epigenetics.

Epigenetic studies are delivering a better understanding of how to tackle some key diseases. This has not only changed how we view the impact of our lifestyle on our own bodies but, remarkably, even on generations to come. Epigenetics changes how genes switch on or off, without changing the DNA sequence. Nevertheless, epigenetic changes are heritable. They not only regulate gene expression in our own cells, and predispose us to certain diseases, but amazingly, these modifications have now been linked to disorders affecting subsequent generations. Let's take a look at how this mechanism of heritability was discovered.

Feast and famine

In 1800, there was a total crop failure in Överkalix, northern Sweden. Harvests were unpredictable for many years after, with periods of crop failure and famine often followed by massive harvests, and the good people of Överkalix gorged themselves during these periods of plenty.



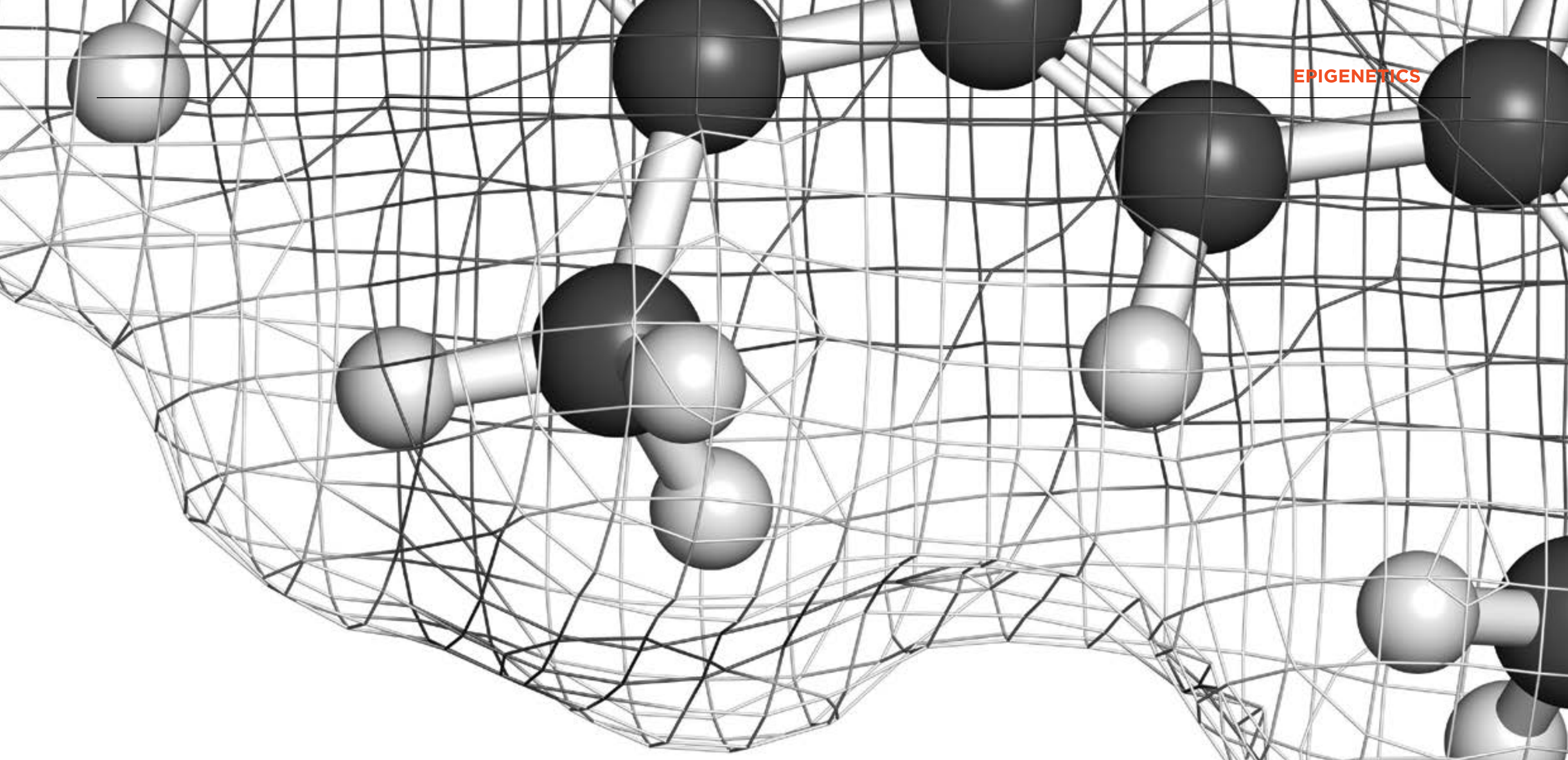
Fast forward to 1984, and Lars Olov Bygren at Sweden's renowned Karolinska Institute was studying the health of the Överkalix population. Looking at births in 1905, Bygren discovered that grandsons of Överkalix boys who had experienced good harvests – going from normal eating to gorging themselves during a single season just before puberty, as sperm were maturing – had an average six year reduction in life expectancy compared with grandsons of Överkalix boys who had experienced famine during the same stage of their development. This reduced life expectancy was often attributed to diabetes and, once the data was adjusted for socioeconomic variations, the difference in longevity jumped to an amazing 32 years! The grandfathers' single season of gluttony somehow affected their grandsons.

Later work showed that the paternal granddaughters of women who experienced gluttony or famine when they were in the womb or before puberty also had dramatically differing life expectancies. This was another example of what Bygren called 'early influences that give late replies'. His discovery clearly showed that these experiences led to heritable traits, but remained unpublished, and it was only when the concept of 'transgenerational responses' was widely accepted almost two decades later that his results received the recognition they deserved.

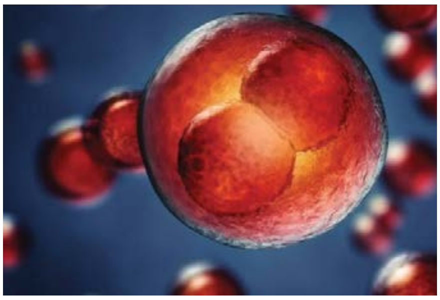
What is epigenetics?

Epigenetics is the study of changes in gene expression that occur without changes in the DNA sequence. Examples include DNA methylation and histone modification, and different cells in the body have specific epigenetic profiles that modify gene expression for the cell's function. These epigenetic changes can persist throughout a cell's life, and even be passed on.

Gametogenesis – the creation of sperm and eggs – is of particular interest in epigenetics research. During development, the fertilized egg forms a blastocyst containing pluripotent stem cells. These cells have the potential to form any cell type – their genetic slate has



been wiped clean – but epigenetic changes from either parent could potentially be passed on. Later, female fetuses form ovaries and egg cells while still in the womb. Astoundingly, this means that at one point in pregnancy, three generations – the pregnant 'grandmother', her unborn daughter whose ovaries are under development,



and the forming eggs which will then be ready to conceive children later in life – are in essence simultaneously exposed to the same environmental stresses, such as famine or gluttony. In contrast, sperm first form during puberty in boys, and so the environment cannot start imprinting epigenetic markers until this time.

Another example of disease-related epigenetic modification was outlined by Dr Kari Nadeau, now at Stanford University. She discovered that children exposed to excessive air pollution were more likely to develop asthma due to epigenetic changes affecting genes which prevent the immune system from overreacting to allergens, such as airborne pollutants. Dr Nadeau showed that immune cells called regulatory T-cells displayed asthma-inducing changes in expression of the *Foxp3* gene, due to epigenetic tags on *Foxp3* which could last a lifetime, and even be passed on.

New insights, novel therapeutic strategies

These examples emphasize the impact our lifestyles have, not only on ourselves, but also on our descendants. Even though epigenetic changes may eventually wear off, smoking, poor eating and toxin exposure can be carried forward in gametes.

Understanding epigenetic gene regulation opens up new possibilities for the development of novel drugs. The first FDA-approved epigenetic drug – azacitidine – was released in 2004 for the treatment of patients with a group of rare and deadly blood malignancies called myelodysplastic syndromes. Azacitidine is thought to inhibit the methylation enzymes that put epigenetic tags on genes in blood precursor cells. Since 2004, the FDA has approved three other epigenetic drugs that might work by stimulating tumor suppressor genes that are epigenetically silenced when the tumor develops. The recent emphasis on epigenetics also extends beyond the pharmaceutical industry. Nestlé has committed to a six year research program to study how epigenetics is involved in maternal and early life nutrition and health.

Some even contend that epigenetics finally reveals the bankruptcy of the overly-simplified concept of 'nature versus nurture'. Continued research will expand our understanding, and reveal more about the role of epigenetics in normal cell function and disease. As our knowledge of epigenetics deepens, the doors will open to a whole new dimension of the mechanisms underpinning human health.

Further reading

Air Pollution Causes Epigenetic Changes That May Trigger Asthma, Discover magazine **http://discovermagazine.com/2015/sept/15-something-in-air**

Why Your DNA Isn't Your Destiny, Time magazine **http://content.time.com/time/magazine/article/0,9171,1952313,00.html**

Dawson, MA; Kouzarides, T. Cancer Epigenetics: From Mechanism to Therapy. *Cell*, 2012, **150**(1), 12-27.