Epigenetics and Beyond

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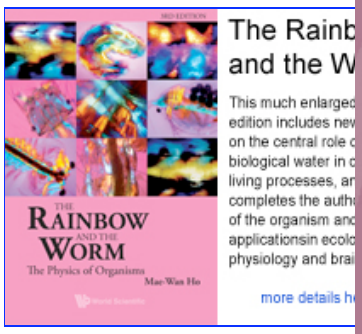
Epigenetic Inheritance

"What Genes Remember"

Epigenetic inheritance of acquired characters more powerful than inheritance of genes

The experience of one generation can modify genes passed on to the next via a variety of mechanisms that blur the distinction between epigenetic and genetic Dr. Mae-Wan Ho

"Sins of the fathers, and their fathers"



The experience of young boys could affect not just their own health in later life, but also the health of their sons and grandsons. The UK research team led by Marcus Pembrey at the Institute of Child Health, University College London published their findings in 2006 in the *European Journal of Human Genetics* [1], accompanied by a News and Commentary piece, "Sins of the fathers, and their fathers" [2].

Two years later, a long feature article, "What genes remember", in *Prospect Magazine* stated [3]: "Many geneticists now think that the behaviour of our genes can be altered by experience – and even that these changes can be passed on to future generations. This finding may transform our understanding of inheritance and evolution."

The significance of the finding is that it departs from well-known and generally accepted environmental effects on the unborn foetus in mother's womb or other maternal effects, mediated by the many provisions in the egg cell during embryogenesis, and after birth, in mother's milk.

In contrast, effects passed on through the *paternal* line are associated with sperm cells that contain very little apart from the father's genes.

Somehow, the father's experience as a young boy appeared to have affected his genes and the changes are transmitted to his male offspring in what appears to be a case of Lamarckian inheritance of acquired characters that still gets many biologists hot under the collar (see Box)..

Lamarck, the scourge of neo-Darwinists

French naturalist Jean Baptiste de Lamarck (1744-1829) is credited with having invented the discipline of biology and also for being the first to propose a comprehensive theory of evolution: organisms evolve through natural means and not through special creation. The two main mechanisms in Lamarck's theory of evolution were: 'use and disuse', use enhances and reinforces the development of the organs or tissues while disuse results in atrophy; and 'inheritance of acquired characters', transmitting to subsequent generations the tendency to develop certain new characteristic that the organism has acquired in its own development. Lamarck's theory preceded Charles Darwin's theory of evolution by natural selection by more than 50 years [4] (see Lamarck the Mythical Precursor, ISIS scientific publication).

While Darwin invoked the inheritance of acquired characters as a subsidiary mechanism to the natural selection of random variations, his modern-day disciples, the *neo*-Darwinists, have strenuously opposed any taint of Lamarckism. They insist that genetic variations – changes in base sequence of DNA – arise by *random* mutations unrelated to the environment or their survival value, which are then subject to environmental selection; those mutants that survive, survive, while the rest die out [5] (see Why Lamarck Won't Go Away, ISIS scientific publication). This belief is encapsulated in Francis Crick's Central Dogma of molecular biology, which decreed that genetic information flows strictly one-way from DNA to RNA to protein (that determine the characteristics of the organism selected by the environment), and never in reverse. In their words, the environment can never pass information *back* to the genes, so acquired characters cannot be inherited.

Since the mid-1970s, if not before, molecular geneticists have been turning up evidence that increasingly contradicts the Central Dogma, and by the early 1980s, the new genetics of the 'fluid genome' had emerged [6] (see Living with the Fluid Genome, ISIS publication). But apart from a few 'heretics', no one dared to say a word against the Central Dogma or the neo-Darwinian theory of evolution which depends on it.

Things have changed a lot since the human and other genomes were sequenced, and deposited in one freely accessible central database [7] (Death of the Central Dogma, SiS 24). The database is not much good for business, or drug discovery [8] (The human genome sellout, *ISIS News* 6), but turns out to be very good [7] "for research that exposes the poverty of the genetic determinism ideology that has led to the creation of the database in the first place."

The 2004 series Life after the Central Dogma [9] (Science in Society 24) marked the end of genetic determinism, and documented why the new genetics demands a thoroughly ecological approach in our public health, environment, and social policies. Research findings since have strongly reinforced this message to policy makers. It now appears that the experience of individuals during critical periods of early development can influence not just their own lives as adults, but those of their children and children's children.

The Avon Study

The UK Avon Longitudinal Study of Parents and Children (ALSPAC) is a long-term health research project involving more than 14 000 mothers enrolled during pregnancy in 1991 and 1992. Analysing data from the study, researchers showed that the sons of fathers who smoked before puberty had a significantly greater body mass index (measure of obesity) at 9 years of age: 18.15 compared with 17.23 in sons of fathers that never smoked [1]. But there was no effect on the body mass index of the daughters.

Faced with this intriguing finding, the research team turned to old records of people born in1890, 1905, and 1920 from Overkalix, an isolated community in Northern Sweden, where previously, they had reported an association of ancestral food supply with longevity and death from cardiovascular disease and diabetes.

Re-analyzing the records showed that the paternal grandfathers' food supply during mid childhood was indeed linked to the risk of

death in grandsons, but *not* in grand-daughters. Poor availability of food was associated with *reduced* risk of death in grandsons by 35 percent while good availability of food was associated with *increased* risk of death by 67 percent compared with controls.

In contrast, the nutritional status of the paternal grandmother had no influence on the grandsons, but affected the granddaughter in a similar way. Good food availability increased the risk of death for grand-daughters by 113 percent, while poor food availability decreased the risk of death by 49 percent.

A previous study on the same ALSPAC database had found an association between high birth weight in grand children and type 2 diabetes in maternal grandparents; but not in paternal grandparent [10].

Epigenetic inheritance

The results of the ALSPAC studies imply that experience during a crucial period of life could influence more than one generation in a sex-specific way.

Although the mechanisms involved in humans are not yet known, this kind of trans-generational effects is being taken more seriously because similar effects - now described as 'epigenetic inheritance' - have been documented in a substantial number of animal studies. For example, how an adult rat responds to stress was found to depend on whether its mother cared for it adequately as a pup, which marks certain genes for the rest of its life [11] (Caring Mothers Reduce Response to Stress for Life, *SiS* 24), and we shall update that fascinating story [12] (Caring Mothers Strike Fatal Blow against Genetic Determinism, *SiS* 41). Another series of studies show that a single exposure of rats during embryogenesis to the fungicide vincozolin is sufficient to cause a range of serious diseases and abnormalities in the adults that are transmitted to three further generations [13] (see Epigenetic Toxicology, *SiS* 41).

Epigenetic change is usually defined as that which does not involve changing DNA sequences, or "the structural adaptation of chromosomal regions so as to register signal or perpetuate altered activity states" [14], but such definition are rapidly becoming obsolete.

In reality, epigenetic modifications encompass a great variety of mechanisms acting not just at transcription but at post-transcription and translation of genetic messages, and indeed, even rewrites genomic DNA itself [15, 16] (see Epigenetic Inheritance through Sperm Cells, and Rewriting the Genetic Text in Brain Development and Evolution, *SiS* 41). Epigenetic mechanisms include various enzyme-catalyzed chemical modifications of genomic DNA (methylation of cytosine residues in CpG dinucleotides) and histone chromatin proteins (methylation, acetylation, phosphorylation, ubiquitinylation, etc.), which recruits other proteins such as transcription factors and repressors, that together, determine the activity state of specific genes or sets of genes [17, 18]. Also included are changes to the genetic messages transcribed [19, 20]. RNA editing systematically alters base sequences, such as changing adenosine (A) to inosine (I), which is read as guanosine (G), resulting in an entirely new message. Alternative splicing creates different proteins; and RNA interference determines which messages are cleaved, or blocked from translation. Transcription factors promoting the expression of certain genes may be involved at the same time in repressing neighbouring genes [19]. Finally, epigenetic mechanisms include reverse transcription of altered transcripts [15, 16], which has the effect of rewriting the genetic messages encoded in genomic DNA, and hence distinctly blurring the boundaries between epigenetic and genetic.

Epigenetic modifications occur in cell differentiation, so that different genes are expressed, different messages are altered, say in brain cells as opposed to skin cells, and they are inherited by the daughter cells in cell division. Most epigenetic changes are 'erased' in the germ cells that produce the next generation (DNA methylation is studied in greatest detail in this respect), but some modifications survive, and are passed on to the next generation. We shall be dealing with different examples in other articles in this series.

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