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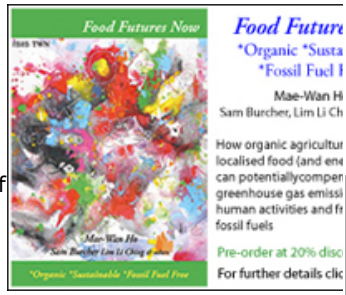
**Epigenetics and Beyond**

# Darwin's Pangenesis, the Hidden History of Genetics, & the Dangers of GMOs

Dr. Mae-Wan Ho *uncovers a fascinating page in the history of genetics expurgated from the mainstream account that also tells us why genetic modification is so dangerous*

## The mainstream account of genetics and its demise




The story of modern genetics typically begins with August Weismann's identification of the 'germplasm' as the stuff of heredity and the re-discovery of Gregor Mendel's hereditary units, or 'genes' controlling the characteristics of organisms, and the rules of inheritance named after him. Thomas Hunt Morgan mapped the genes to linear strings on chromosomes. A frantic search for the identity of the genetic material culminated in the DNA double helix, which neatly explained all the properties required of a genetic material. DNA replicates faithfully and is passed on largely unchanged to the next generation; it gives rise to variations by rare random mutations; it controls the characteristics of organisms by coding for proteins, and undergoes recombination according to the rules worked out by Mendel and Morgan.

Francis Crick's Central Dogma of Molecular Biology - that genetic information passes one-way from DNA to RNA to protein - became the ruling paradigm of molecular genetics from the 1950s up to the mid-1970s. It encapsulated the genetic determinist ideology that led up to it, or rather, projected backwards from it, to trace out the linear progression of historical advances that serves to validate the present. This is what I mean by the mainstream account.

But soon after genetic engineering began in the mid-1970s, geneticists were to find exceptions and violations to every tenet of classical genetics and the Central Dogma. In direct contradiction to the concept of a relatively static genome with linear causal chains emanating from genes to the organism and the environment, they discovered constant cross talk between genes and environment. Feedback from the environment not only determines which genes are turned on where, when, by how much and for how long, but marks, moves and changes the genes themselves. By the early 1980s, 'the fluid genome' had emerged to make genetic determinism obsolete (For more details see [1, 2] (Genetic Engineering Dream or Nightmare, and Living with the Fluid Genome, ISIS publications).

In the years following, and especially since the human genome sequence was announced, the mainstream account became even more untenable [3] (see Death of the Central Dogma and other articles in the series, *SiS* 24).

Evidence of the inextricable entanglement between the organism and its experience of the environment is forcing us to rethink not only genetics, but evolution [4, 5] (Epigenetic Inheritance - What Genes Remember, *SiS* 41; Development and Evolution Revisited,



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ISIS scientific preprint). The phenomenon of 'epigenetic inheritance' indicating that experience during a crucial period of an individual's life could influence subsequent generations, is nothing short of the 'inheritance of acquired characters', a mechanism of evolution attributed to Lamarck. Lamarck was the subject of ridicule and derision in the mainstream account; as opposed to Darwin, whose theory of evolution by natural selection has remained unquestioningly revered to this day. So, was Darwin mistaken?

## Darwin's Lamarckian tendencies

As every serious student of evolution knows, Darwin did subscribe to the inheritance of acquired characters as an important subsidiary mechanism to natural selection; it was only his followers, the neo-Darwinists who were vehemently opposed to it [5]. And since the first publication of his *Origin of Species* in 1859, Darwin became more and more absorbed in the idea.

In 1868, Darwin put forward the theory of Pangenesis to account for the inheritance of acquired characters. He suggested that all cells of an organism shed minute particles, or gemmules, which circulate throughout the body and are passed on to the nest generation through the germ cells, thereby transmitting the characteristics of the parents to their offspring. *And if the cells of the parents undergo changes during their life time, those changes would also be transmitted to the offspring*.

Darwin's cousin Francis Galton designed a series of blood transfusion experiments on rabbits with different pigments to test the theory of Pangenesis, or at any rate, to test if gemmules existed; but found no evidence for them, and the theory was largely abandoned.

Within the past decade, geneticists have discovered substantial amounts of nucleic acids circulating in the bloodstream which are taken up by cells and transported to the nucleus, where they could be integrated into the cells' genome (see [6, 7] Latest Exposé on the Fluid Genome, *SiS* 15; Intercommunication via Circulating Nucleic Acids, *SiS* 42)). These nucleic acids appear suspiciously like Darwin's gemmules.

Liu Yongshen at the Henan Institute of Science and Technology in Xinxiang, China, described Darwin's theory of Pangenesis in some detail and reviewed both historical and more recent evidence in support of it, referring to fascinating findings on blood transfusion that have been expurgated from the mainstream account. He concluded that [8] "a considerable revision of views on Darwin's Pangenesis must occur before a new comprehensive genetic theory can be achieved."

## Darwin's Pangenesis and Michurinist genetics

Darwin recognized that cells multiply by division, and preserve their nature, thus accounting for cell heredity. But it could not explain phenomena such as the effects of use and disuse (another Lamarckian mechanism of evolution), the inheritance of acquired characters, graft hybridization (hybrids created by grafting), which required some means of transferring heritable characteristics. Other phenomena in need of explanation were variation, development, regeneration, and reversion (atavism), which required the hereditary influence to change, and to remain dormant until activated.

Darwin proposed therefore that cells not only grow by means of cell division, but are also able to throw off minute particles (gemmules) that self-replicate, move through the body, can vary in response to the environment, and are capable of dormancy. Furthermore, cells can throw off gemmules throughout development, and these gemmules can enter the buds and germ cells, and that is how they can influence the development of the offspring. If the cells of one part of the body underwent changes as a result of environmental change, they would throw off modified gemmules that could also be transmitted to the offspring, and account for the inheritance of acquired characters, and many other phenomena.

Gemmules released in a stock plant would be transferred into a graft and become incorporated into the germ cells and meristems

(growing points) of the graft, resulting in heritable changes in the graft and its progeny. This would account for graft hybridisation, the subject of 'Michurinist genetics' (see below).

Gemmules, like seeds or spores, can be transmitted in a dormant state, allowing a character to be expressed after several generations. Thus, reversion is explained as the result of long-dormant gemmules becoming active. A reserve of gemmules in the tissues could give rise to regeneration of lost parts, and malformations and monstrosities could be due to gemmules reaching the wrong destinations in the offspring. The fact that mutilations are not transmitted by inheritance is explained by the presence of sufficient gemmules from the previous generations. Characteristics that appeared only at a certain stage of development were explained as the result of interactions between the developing cells and gemmules.

Most of all, Darwin saw the theory of Pangenesis providing an explanation of how variations can arise upon which natural selection could act. And in that regard, he was closest to Lamarck [5].

Ivan Vladimirovich Michurin.(1855-1935) was a distinguished Russian geneticist and horticulturist whose work was appreciated and promoted by Lenin. After his death, Michurin was co-opted by Lysenko for a repressive political and social campaign and propaganda war under Stalin. Michurin was hailed as the true follower of Darwin responsible for "productive Soviet Michurinist Biology", as opposed to the "fruitless capitalist Weismannist-Morganist-Mendelist genetics" of Western Europe and the United States [9]. This had done nothing for Michurin's true contribution to biology, and at the same time, deepened the stigma attached to Lamarckism.

Scientifically, Michurin, *was* true to Darwin, in that like Darwin, he did believe in the primary role of natural selection while subscribing to the importance of the environment and Lamarkian inheritance of acquired characters. Michurin created new fruit plants throughout his life using graft hybridisation, introducing more than 300 new species. His fruit garden was admired by Lenin, and he was awarded the Order of Lenin and Order of the Red Banner of Labour [9].

## Interspecific hybridisation by blood transfusion

Francis Galton failed to find any evidence that transfusing blood from white into silver-grey rabbits and *vice versa* could change the coat colour of the offspring, as expected, if the respective gemmules were present in the blood. But subsequent experiments produced overwhelmingly positive results, though not reported in the mainstream account of genetics.

Inspired by Michurin's investigations on graft hybridisation in plants, Russian biologist P.M. Sopikov began to re-investigate the effect of blood transfusion in a series of experiments starting in 1950.and well into the 1970s.

In the first experiment, blood from the Black Australorp roosters was transfused into White Leghorn hens, which were then mated with White Leghorn roosters [10]. Injections of 2.5 to 3 ml blood per kg were given twice weekly for two and a half months before the fertilized eggs were laid. When these eggs hatched, some of the progeny were found to have several black feathers in their white plumage.

A similar experiment was carried out with White Leghorn donors and Black Australorp recipients. White feathers appeared in the otherwise black plumage of the progeny. There were also other changes. Compared with the purebred controls, the experimental birds showed an increase in body mass, larger neck and body size, longer legs and abnormal leg pigmentation. The egg shell colour of some of the experimental White Leghorn resembled Black Australorps.

These changes became more marked in each successive generation of treatment. In the third generation, the birds had white plumage, or white with black feathers, light-grey to grey, or became black like the donors.

Blood from Chuvash geese injected in White Leghorn and Khaki Campbell ducks as recipients, or blood from Bronze turkey injected into White Leghorn recipients, all resulted in abnormal characters in the progeny. The blood transfusion itself was found to increase viability, productivity, reproductive efficiency and body mass of recipients and their progeny, eliminating the adverse effects of inbreeding and facilitating hybridization between species, exactly as in the case of graft hybridisation in plants.

The Leningard White and Leningard Black breeds were created by blood transfusion between White Leghorns and Black Australorps over three generations, followed by interbreeding and selection. A heavy type of Leningard White fowl with males weighing 4-5 kg and females 3.3-3.5 kg was created in the same way.

Sopikov's findings were confirmed by many Soviet researchers. Reports of the success achieved by Soviet biologists reached geneticists in other countries. Similar experiments were conducted in France, Switzerland and elsewhere with comparable results. For example, blood from guinea fowl injected into a strain of Rhode Island Red chickens gave progeny in the first and second generations with extensive changes in the quantity and distribution of melanin pigment in the plumage [11]. The transmission of modifications continued to the seventh generation after a single series of injections of guinea fowl blood. However, some investigators failed to induce heritable changes in chickens by blood transfusion. Among 50 reports on blood transfusion collected by Liu [8], 45 showed positive results and only five had negative results.

So why did Galton fail to find such effects in his experiments? Liu suggested blood group incompatibilities, or else the volume of blood transfused may have been insufficient. Bird red blood cells are nucleated whereas mammalian red blood cells are not, which would reduce the amount of transforming DNA present.

## DNA induced heritable transformations

As is well known in the mainstream history of genetics, Avery, Macleod and McCarty were the first to describe transformation of bacteria by foreign DNA in 1944 [12], thus providing the first proof that DNA was the genetic material, and not protein, as was then widely believed.

What's missing from the mainstream account is that subsequently, a successful induction of heritable changes in the Pekin duck was demonstrated using DNA from the Khaki-Campbell duck. Moreover, the treatment of recipient ducks with erythrocyte DNA not only induced hybridization in the progeny, but also affected the recipient parents [13]. The majority of the treated birds and their offspring developed a range of characters (pigmentation of beak, feather morphology, head shape, body conformation and size) that apparently resembled the donor breed. Heritable modifications of morphological characters in ducks as a result of DNA and RNA injection from other breeds of ducks were also report by other workers [14].

In 1995, Japanese researchers reported that a single intravenous injection into pregnant mice of a plasmid (replicating piece of DNA outside the genome in cells) genetically modified to express a foreign gene in a complex with lipopolymine was sufficient to transfer the gene into the embryos [15]. A few years later, researchers in Germany [16] demonstrated that viral or bacterial plasmid DNA fed to mice during pregnancy could be detected in cells of the foetuses and the newborn.

Within the past decade, geneticists have discovered substantial amounts of DNA and RNA circulating in the bloodstream and fluid surrounding cells [7]. The circulating DNA binds to receptors on the surface of living cells and is taken up and transported to the nucleus and incorporated into the genome. The ease with which nucleic acids are taken up by living cells, widely exploited in experiments in 'gene therapy', highlights the potential hazards of the huge amounts and diversity of genetically modified nucleic acids released into the environment and into our food chain [17] (*Slipping through the regulatory net*, ISIS/TWN publication).

## Environment-induced changes to DNA and RNA transmitted through germ cells

The numerous experiments in birds, like those in bacteria, showed that donor DNA injected into and circulating in the bloodstream of recipients could indeed transform the recipient and its offspring, behaving rather like Darwin's gemmules. Consequently, any change to the DNA and RNA circulating in the individual's blood stream would also be expected to transform the individual and its offspring.

We now know that environmentally induced changes to both DNA and RNA are part of normal development, especially prominent in the central nervous system and the immune system, where a great deal of research has been done [18] (see Rewriting the Genetic Text in Human Brain Development, *SiS* 41). One major mechanism is RNA editing induced by specific environments that systematically alters the genetic messages transcribed from the genome by changing its base sequence, thus creating new proteins, new RNA species that regulate the expression of whole sets of genes. Genomic DNA of cells can be rewritten by reverse transcription from the RNA altered as the result of specific experiences of the environment. Thus, in the course of an organism's life, its complement of circulating nucleic acids will be changing according to its unique experiences. These changes are constantly communicated to other cells of the body via the circulatory system. They may also be passed on to the germ cells to influence the next generation. The circulating nucleic acids may pass through the placenta to the cells of the embryos [15, 16]. There is also evidence that sperm cells may be particularly adapt at taking up circulating nucleic acids and transferring them to the egg during fertilization [19, 20] (Epigenetic Inheritance through Sperm Cells, the Lamarckian Dimension in Evolution, *SiS* 42).

## Horizontal gene transfer denied and dismissed by proponents of GMOs

What are the implications of these findings now that Darwin's theory of Pangenesis has been restored to its rightful place in the history of genetics?

In the 1990s, a few colleagues and I found ourselves fighting a lonely battle warning regulators and the scientific community about the dangers of horizontal gene transfer from the rampant creation of GMOs and GM constructs [17 19] (Gene Technology and Gene Ecology of Infectious Diseases, ISIS Scientific Publication).

A major hazard inherent to GM is indeed enhanced horizontal gene transfer and recombination. There are many reasons for suspecting that is the case (see [20] (Horizontal Gene Transfer from GMOs Does Happen, *SiS* 38), of which I shall mention only two. First genetic modification involves making artificial synthetic combinations of nucleic acid sequences that had never existed in billions of years of evolution; these recombinant sequences are highly mosaic, with similarities to a wide range of species including pathogenic bacteria and viruses; hence they are more likely to take part in horizontal gene transfer and recombination. Second, GM constructs are designed to invade genomes with recombinogenic ends; this makes them inherently unstable and more likely to move again once integrated, and there is evidence both for transgenic instability [21] (Transgenic Lines Unstable hence Illegal and Ineligible for Protection, *SiS* 38), and horizontal transfer of transgenic DNA [20].

Horizontal gene transfer and recombination not only create new disease-causing bacteria and viruses, but also spread antibiotic resistance marker genes in transgenic DNA, making infections untreatable. Integration of foreign DNA into cells can disrupt genes, cause cancer, and reactivate dormant viruses that are in all genomes.

These potential hazards take on new significance in the light of the DNA and RNA found circulating in the bloodstream and extracellular fluids of both healthy and diseased individuals, and the ease with which they are taken up into cells [7, 17]. Genetic modification is indeed more dangerous than the intentional creation of biological agents simply because its hazards are underestimated by practitioners and regulators alike [22] (No Biosecurity without Biosafety, *SiS* 26). It must be strictly confined and contained in laboratories. There is no need and no case for continuing to

release GMOs into the environment.

It is not only Darwin's theory of Pangenesis that's in need of rehabilitation in the bicentenary of his birth. The entire history of genetics and its continuity with epigenetics need to be truthfully retold, to put an end to the abuses and misuses of the subject that endanger society.

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**Louis Krut** Comment left 15th April 2009 21:09:11
Dr. Wang Ho: Thank you (again) for keeping at us. In our age, in which the giant corporations rule the world, it is difficult to overcome their influence. Our only weapon is knowledge, and your mission to keep us informed provides the best chance we have of surviving in a form we would recognise. We might not be the best there could be, but we are the best we know. We cannot know what alternative(s) might be generated and that should frighten us enough to stop our mad charge into areas best left unexplored. It is an old lesson, but one we have not yet learnt.

**Rory Short** Comment left 15th April 2009 21:09:09
It is a great relief to hear that genetic science has caught up with my gut feeling that genetic engineering is a dangerous activity especially when the GMO's are released into the environment.

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