

# Environment and fetal programming: the origins of some current “pandemics”

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*From the womb to the adult*

**Guest Editors: Vassilios Fanos (Cagliari, Italy), Michele Mussap (Genoa, Italy), Antonio Del Vecchio (Bari, Italy), Bo Sun (Shanghai, China), Dorret I. Boomsma (Amsterdam, the Netherlands), Gavino Faa (Cagliari, Italy), Antonio Giordano (Philadelphia, USA)**

*“The womb may be more important than the home”*  
David Barker

### Keywords

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It has been well known for many years that prenatal life is not fully protected in the uterine microenvironment. But only over the last decade we have been focusing on mechanisms and modalities of maternal and foetal exposure to an impressive range of chemicals (e.g.: endocrine disruptors) [1], physical factors (e.g.: ionizing radiations) [2] and biological agents (e.g.: viruses) able to induce potentially adaptive and predictive epigenetic changes in the embryo-fetal genome, thus interfering with the programming of tissues and organs in an often irreversible way. Sometimes these epigenetic marks could be even inherited from one generation to another [3]. This new awareness could radically transform the representation of the individual development (ontogeny) and of the evolution of our species (phylogeny) [4, 5].

In particular, on these bases, a new model of pathogenesis is outlined which can explain in a more exhaustive way the ongoing increase of chronic-degenerative, inflammatory and neoplastic diseases that we could define as the Epidemiological Transition of the XXI Century: in fact, cardiovascular [6, 7] and endocrine-metabolic disorders (obesity, metabolic syndrome, insulin resistance and diabetes II) [8-10]; immune-mediated diseases (allergy [11, 12], celiac disease and autoimmune diseases [13]); neuro-developmental [14, 15] and neurodegenerative disorders [16] (autism, ADHD, Alzheimer disease) and many types of cancer [17-19] are rapidly increasing all over the world in relation to the degree of industrialization [20, 21].

This model of pathogenesis is the so-called theory of the embryo-foetal origins of adult diseases (DOHaD: Developmental Origins of Health and Diseases) which is based on an amazingly simple and universal mechanism: the information coming from the environment (through the mother and the placenta) can modulate the whole developmental process of the foetus, by inducing its cells to differentiate in a predictive and adaptive way [22]. If the foetal programming is disturbed by pollutants or if there is a mismatch between the information received by the foetus and the actual postnatal environment the result can be the increase of chronic diseases we are witnessing [23], that could even concern the subsequent generations if the flawed epigenetic marks concern the germ cells [24].

In order to better understand the revolutionary impact of this new pathogenic paradigm, we have to underline that the building of the phenotype is not the direct product of the program encoded in our DNA but the effect of the interaction between

the information coming from the environment and the one potentially inscribed in the DNA [25]. This also means that while the sequence of DNA (the *hardware*) [26] is very similar in each individual of our species (being the product of the *phylogeny*), the epigenome (the *software*), which is the product of the *ontogeny*, is very different in every cell and in every individual, thus causing the great physiological and pathological variation of human phenotypes.

The epigenome is, in fact, the fluid, dynamic component of the genome, able to acquire a memory of the experiences, thus giving the individuals the opportunity to better adapt to the environment. Some cell types, in particular those of the central nervous system (neurons and glia) [27] and those belonging to the immune system (lymphocytes) [28, 29], have a greater ability in acquiring molecular memory both epigenetically and genetically, maintaining a great plasticity during all life. This is very important, but can become very dangerous for our health [30, 31].

However, the most interesting findings concern the germ cells. In the past germ cells were supposed to be isolated and unable to be modified by the information coming from the environment (Weismann Barrier). But it is more and more evident, and even upsetting, that both male and female gametes are exposed to external information [32, 33] and able to modify both their epigenome and their genome paving the way for a transgenerational transmission of new characters and, as stated above, of pathological phenotypes [34].

The period of the ontogenesis is obviously, in this perspective, the most important of our life: both because of the great developmental (epigenetic) plasticity of poorly differentiated cells and tissues and because of the inevitable amplification of the effects, in the postnatal life, of the early *epimutations* that make up the *foetal programming*.

It is important to realize that our phenotype is programmed for life by this complex process, partly genetically programmed through millions of years of evolution, partly induced by the information coming from the environment through the modulating action of the placenta [35]. The very fact that our organism is composed of trillions of cells all descending from a totipotent cell (zygote) and containing an almost identical DNA, yet morphofunctionally very different (the human body being composed of more than 200 different cell types), reveals the crucial importance of the *epigenome* and of the *foetal programming* in building our (both physiological and pathological)

phenotype. All these considerations made the scientists understand they had to redesign the fundamentals of Genome Project [36-38].

The waddingtonian essence [39] of this process is now widely accepted and demonstrated in molecular terms as well as the particular sensitivity of the developing organism both to the physiological signals (morphogens) and to the potentially harmful information coming from the environment in the very first stages of organogenesis (*windows of exposure*). Among the most known epi-genotoxic agents able to induce alterations in the DNA methylation and, therefore, to disrupt the endocrine-metabolic programming, there are: heavy metals (particularly arsenic) and other “endocrine disruptors” such as bisphenol A [40, 41], genistein [42], vinclozolin [43], methoxychlor, TCDD and diethylstilbestrol (DES) [44]. In particular, experiments with vinclozolin and TCDD produced transgenerational effects in laboratory animals [45].

If we want to understand how this new pathogenetic paradigm (DOHaD) was conceived it could be useful just to recall which were the fundamental steps in this research [46]. In the 80s and 90s several studies showed significant correlations between low birth weight (a non-specific index of prenatal distress) [47, 48] and an increased incidence of heart diseases, hypertension, obesity, metabolic syndrome, type 2 diabetes and even neuropsychiatric diseases [49, 50] in adulthood. Some scientists supposed a connection between different situations of foetal distress and an altered (epigenetic) programming of organs and tissues [51, 52]. Nowadays the above mentioned epidemiological transition characterized by a general increase in obesity and type 2 diabetes, autism spectrum disorders and neurodegenerative diseases, allergies and autoimmune disorders, cancer may be explained by such a collective and transgenerational mechanism rather than by a genetic one.

This new paradigm is important not only to explain in a more exhaustive way the embryo-foetal origins of all the above mentioned disorders and their dramatic increase over the last decades, but also to try to effectively face this epidemiological transition. The key-term in this context is certainly primary prevention: only by reducing the maternal-foetal factors of distress and the exposure of the foetus (and of its gametes) to pollutants, it would be possible to protect the correct programming of cells, tissues and organs.

## Declaration of interest

The Author declares that there is no conflict of interest.

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