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Epigenetic impact on children's future

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ABSTRACT

The adult diet and lifestyle are conventionally considered at the origin of cardiovascular and metabolic diseases that occur during life time. The hypothesis that supports the link between intrauterine malnutrition, prematurity, maternal stress, and the occurrence of type 2 diabetes and ischemic heart disease in adults/elderly, called Developmental Origins of Adult Disease, has been supported by numerous clinical studies. The concept of fetal phenotype programming gained consistency through epigenetic studies that showed how DNA methylation changes, histone changes, maintained over time are at the origin of chronic adult diseases. Initially demonstrated through studies on experimental animals and later through research on human subjects exposed to extreme situations, epigenetic changes were identified in severe maternal malnutrition, folic acid deficiency, smoking and maternal obesity or contact with environmental toxins. It is possible for some of the epigenetic changes to be transgenerational transmitted, their argumentation subject to objective limitations.

Keywords: fetal malnutrition, coronary disease, type 2 diabetes, obesity, epigenetics

A RETROSPECTIVE LOOK

The onset of type 2 diabetus mellitus and cardiovascular disease has been classically attributed to the specific risk factors in mild-adult life. A shocking hypothesis at the end of the 20th century was the link between gestational/ maternal nutritional deficiencies and of the infant, and chronic pathology of adulthood. Developmental Origins of Adult Disease [DOHAD] known as the Barker Hypothesis [1-3] presented studies on the population of England and Wales from the beginning of the 20th century, Barker and Osmond [2] showed that the poorest areas, with the highest infant mortality had the highest percentage of ischemic heart disease in the adult population. Since prematurity and malnutrition reflect the influence of the environment on pregnancy and the childhood period, the authors hypothesized that they initiate the physiopathological changes that lead to the appearance of late cardiovascular pathology. The effects of fetal origin are focused on the concept of latency in the appearance of some diseases and on the idea of possible genetic changes as a support of pathogenesis. In developmental biology, "early" fixed influences are known as "programming". They focused on deficient intrauterine nutrition, low birth weight, increased insulin resistance, corticosteroid and growth hormone secretion disorders. The economic phenotype, the biological biological product of a poor nutritional environment offers the fetus an adequate adaptation to poor living conditions. If the extrauterine environment offers much more food, the consequences will be obesity and type 2 diabetes. In China, adults who were exposed in utero to the famine of the 1950-1960 period had a high prevalence of hyperglycemia in the conditions of the transition to a western-type diet (18.9%) and increased risk of metabolic syndrome [4,5]. In India, subjects who were born under 2500 g and who came from mothers weighing under 45 Kg developed, over time, in a high proportion (20%) disorders of the glycemic balance and coronary heart disease [6]. The association between low weight at birth and coronary heart disease was confirmed in a cohort study of 15,000 people born in Uppsala, Sweden [7]. A significant association between the weight index at birth (Kg/m^3) and the incidence of diabetes studied by Lithell et al showed a prevalence of the disease 3 times higher in adults born with low weight [8] (Table 1).

The link between nutritional deprivation during pregnancy and subsequent pathology was studied in the Netherlands after the food embargo imposed

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TABLE 1. Prevalence of type 2 diabetes by Ponderal index at birth among 60-year old men in Uppsala, Sweden after Lithell et al, 1996 [8]

Ponderal index at birth (kg/m³)	No. of men	Prevalence of diabetes (%)
<24.2	193	11.9
24.2 to 25.8	193	5.2
25.9 to 27.3	196	3.6
27.4 to 29.3	188	4.3

by Germany in the 2nd World War, between November 1944 and May 1945 [9]. During this period of famine, the food ration dropped to 25% of what was needed, but remarkably, the health registers were kept intact. Sixty years later, those born in that period were subjected to studies regarding cardiovascular and metabolic pathology and the epigenetic changes that occurred, compared to subjects who were not subjected to dietary restrictions. The authors reported the link between undernutrition in the periconceptional period and hypomethylation of the IGF2 gene, possibly through the deficiency of methyl group donors from food amino acids [10].

THE ROLE OF EPIGENETIC CHANGES IN PATHOLOGY

Starting from Barker's studies on the relationship between birth weight and the diseases in mature life and in old age, numerous research was carried out on the phenotypic and biochemical characteristics of children born with low weight, those who are malnourished or from severe maternal stress and the characteristics of pathology in adult life [11-16]. The programming of the fetal phenotype suggested by these studies does not represent the alteration of the genotype but changes in gene expression (DNA methylation, changes in histones and non-coding RNA), belonging to epigenetic changes [16,17].

> *"Epigenetics has proposed to bridge the gap between the environment and phenotype. Epigenetics involves the study of heritable changes in gene expression, which occur without changes to the underlying DNA sequence. Different types of epigenetic modifications include DNA methylation, post-translational histone modifications and non-coding RNAs. Increasingly changes to the epigenome have been associated with early-life exposure in both human and animal models, offering both an explanation for how environment may programme long-term health, as well as molecular changes that could be developed as biomarkers of exposure and/or future disease."*
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> Yamada and Chong, 2017 [17]

It is known that the degree of DNA methylation changes during life: the level of methylation of the genome decreases with age, but some regions of the genome, such as CpG islands, increase their degree of methylation during the aging process. To these changes are added some products by pathological or potentially pathological processes such as malnutrition, stress, toxics, which have a counterpart in clinical changes. The paradigm shift in the etiopathogenesis of cardiovascular diseases starting from programming from a young age can be contested by a number of factors:

- If the correlations between the disorders in fetal life and the pathology installed after an asymptomatic interval of 60-70 years can be considered significant;
- Retrospective studies may become uncertain in value due to a long period of time since the changes were made;
- What is the current value of some data recorded at the beginning of the 20th century for people who will become elderly in the years 2050-2060?
- If maternal stress and poverty can generate changes in fetal/neonatal programming expressed after many years of life
- The objective inability to conduct prospective studies on human subjects to assess health status from birth to death

The existence of an "epigenetic memory" related to histone modifications, DNA methylation and RNAm expression has been attested by numerous experimental research on animals and by some clinical studies. The exposure of rodent embryos to an agricultural fungicide, vinclozin, leads to a decrease in spermatogenesis not only in the exposed animals but also in the following generations (F1-F4) by changing the methylation pattern of the germ line [18]. In rodents, caring for the young through careful maternal tactile contact leads to a modest response to stress. Chicks deprived of maternal care show DNA methylation of the glucocorticoid receptor at the level of the hypothalamus and an exacerbated response to stress in the following periods of life [19]. The epigenome intervenes between the genome and the environment by modulating the functioning of genetic code to allow the genome to produce different phenotypes depending on the structure of the organs, the demands of the environment and the pathology induced by it [20]. Numerous studies have highlighted that non-genetic heredity is an important cause of the occurrence of widespread diseases in the human population.

Epigenetic epidemiology includes the transmission of epigenetic changes through intercellular relays during the individual's life, but also the inheritance from one generation to another (intergenerational) of some pathology determinants [21,22].

Direct epigenetic effects

They have been identified in disorders of imprinting (the imprinted genes come from one parent, that is, only the gene from the other parent is expressed). Genomic imprinting depends on the parent carrying the genetic defect; among which the most studied are: Beekwith Weidemann, Prader-Willi/ Angelman and Silver Russel syndromes (Table 2).

TABLE 2. The effects of methylation disorders in some of the genetic syndrome

Syndrome	Clinical manifestations	Mechanisms
Beck-Wiedeman	Macrosomia, macroglossia, visceromegaly, omphalocele	Errors on the short arm of chromosome 11 (11p15) with methylation disorders of the IgF2, H19 genes
Silver-Russel	Low birth weight, fail to grow and gain weight, a small, triangular face, small jaw, delayed development	Changes in methylation involving the H19 and IGF2 genes, which are located at 11p15

Numerous other diseases have an important epigenetic component through methylation changes of DNA (epimutations), histones, or RNAs. This category includes nutritional disorders, cardiovascular diseases, mental or neoplastic diseases, pharmacological treatments, unhealthy habits (smoking, drugs).

Folic acid deficiency of mothers in the preconception period can be at the origin of neural tube defects [23,24] and possibly of congenital heart malformations and low birth weight [25]. Periconceptional supplementation with folic acid significantly reduces the risk of neural tube malformations [24]. Folic acid is involved in the synthesis of methionine and indirectly in maintaining the DNA conformation and the methylation pattern through its role as a donor of methyl groups.

Maternal smoking during pregnancy severely affects the child's development and pathology both during the neonatal period and afterwards. The effects are evident early through low birth weight and in childhood, adolescence and adulthood through obesity, high blood pressure, insulin resistance, type 2 diabetes, metabolic syndrome [26]. The methylation changes induced by the toxic action of nicotine affect many sites, are maintained for a long time or are extensive, being at the origin of the metabolic pathology of affected children [26]. Smoking is a major risk factor for many types of cancer, in the foreground being lung cancer which provides a risk of death of over 90% in smokers [27]. The epigenetic changes produced by smoking are produced by the hypermethylation of tumor suppressor genes that occur in non-tumorigenic lung tissues [28].

Socioeconomic status. Socioeconomic position (SEP) is a major determinant of health across the life course, but little is known about the biological mechanisms explaining this relationship. Some hypothesis establishes a connection between SEP and gene expression through changes in DNA methylation [29-31]. On a cohort of women from the US, Tehranifar et al [32] examined whether indicators of early life and adult SES were associated with white blood cell methylation. Low family income at birth was associated with adult DNA methylation changes and suggest that there association may be different from adult SES influences on adult DNA methylation.

> *"In humans, low SES across the life course is associated with greater diurnal cortisol production, increased inflammatory activity and higher circulating antibodies for several pathogens, all suggesting a dampened immune response. Recent evidence suggests that DNA methylation of pro-inflammatory genes may be implicated in the biological embedding of the social environment. Our findings support the hypothesis that the social environment leaves an epigenetic signature in peripheral blood cells. Although the functional significance of SES-related DNA methylation is still unclear, DNA methylation might potentially link socioeconomic status to chronic disease risk"*
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> Stringhini S, Polidoro S, Sacerdote C et al. Intern J Epidemiol. 2015:1320-1330

Research carried out in the Philippines on 489 participants with modest socioeconomic conditions highlighted changes in the methylation of inflammatory genes in young adulthood. These would be predicted by early life nutritional, microbial, and psychosocial exposures in infancy and childhood [33]. To evaluate functional biological relevance, authors tested for association between DNAm and inflammatory biomarkers (CRP, IL-6, TNF-α, IL-10, IFNγ, IL-1β, IL-8), and they found that magnitude of many association was substantial with cytokine concentrations that differed by 8.3-75,0 for individuals with low versus high levels of DNAm [33]. The follow-up of a cohort of 241 mother-child pairs of Mexican-American origin through umbilical cord blood samples sought to find if the low standard of living, food and education deficiencies influenced the DNA methylation status of the newborns. The study showed the existence of a weakly positive association between modest living conditions and

DNA methylation changes, without a strong association between socioeconomic conditions and DNA methylation of infants [34]. In the Mexican Pima Indian population 5.6% of men and 8.5% of women had diabetes, while in the Pima community in the USA 34.2% of men and 40.8% of women had the disease, simultaneously with a high incidence of obesity [35]. The low prevalence of type 2 diabetes and obesity in the Pima Indians in Mexico than in the US indicates that even in genetically prone populations, their development is determined mostly by environmental circumstances [35] (Figure 1).

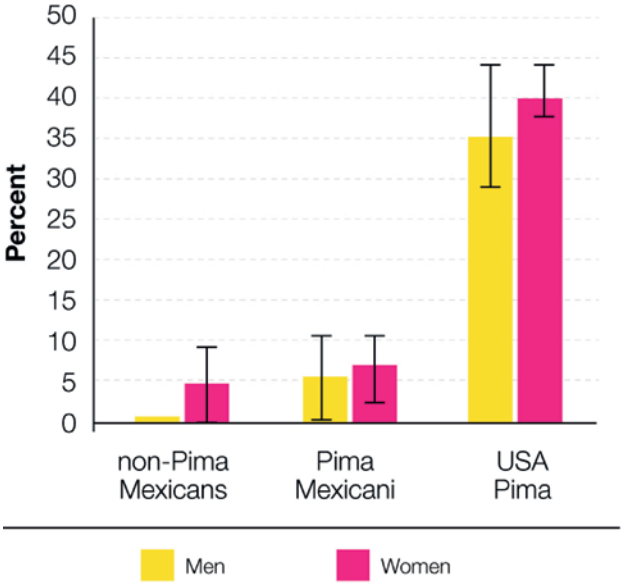

FIGURE 1. Type 2 diabetes frequency in Non-Pima Mexicans, Mexican Pima Indians and Pima Indians in the USA. According to Schultz et al, 2006

Maternal nutrient excess modifies the functioning of epigenetic relays and genes involved in metabolism and have been amply demonstrated by studies on experimental models, such as Agouti mice [31]. DNA methylation of the key genes of adipogenesis is considered a basic mechanism in shaping the phenotype of the offspring of obese mothers [36]. Studies on the link between maternal obesity and the epigenetic changes of the child are difficult due to the difficulties in accessing the target organs. Usually, the DNA methylation level is considered a surrogate parameter for the organism as a whole [36]. A study on 903 mother-child pairs from low-income families in the USA included pre-pregnant obese mothers and their children by determining DNA methylation in umbilical cord leukocytes to determine if their changes influence children's obesity at the age of 18. The results showed a significant effect of the link between maternal obesity and child overweight/obesity [37].

Environmental toxicants. In many communities, children and adults are exposed to high levels of toxicants, despite the fact that these compounds have a well-known health impact [12]. Some chemicals have a direct impact on health, while others produce epigenome changes manifest over one or more generations (Table 3).

TABLE 3. Effect of environmental chemicals on pathology via epigenetic changes. After Hou et al [38], modified, after Hauptman, modified [39]

Environmentals chemicals	Main epigenetic modification	Example of disease potentially associated with epigenetic changes
Nickel Cadmium Chromium Aluminium	Changes in DNA methylation	Various cancers
Arsenic	Changes in DNA methylation	Anemia, gastrointestinal effects, neurotoxicity
Lead		Developmental delays, learning disabilities, anemia, kidney function
Mercury	Changes in DNA methylation	Neurotoxin, development delays, behavioral disorders, autism
Pesticides	Changes in DNA methylation	Neurotoxic effects, various cancers, schizophrenia
Benzene	Changes in DNA methylation	Various cancers, psoriasis
Bisphenol A	Changes in DNA methylation	Long lasting effects on brain function, behavior, neurodevelopment
Dioxin	Changes in DNA methylation Changes in histone modification	Russell-Silver syndrome, brest, colorectal, gastric cancers

Transgenerational epigenetic effects

Transgenerational epigenetic inheritance represents the transmission of epigenetic markers (pollutants, chemicals, pathogens, parental care) that influence fertility, metabolic functions, behavior, in the following generations in the absence of direct environmental influences [18,40,41]. Epigenetic markers are eliminated in 2 phases through demethylation and remethylation processes before fertilization. However, a subgroup of genes that carries parental methylation imprints evade reprogramming mechanisms and can transmit transgenerational epigenetic inheritance [11,18,19]. Previously mentioned, the transmission of epigenetic markers was demonstrated on rodents after prolonged contact with agricultural fungicides through the apoptosis of testicular germ cells, the decrease of spermatogenesis over the next 3 generations [18]. Transgenerational effects were accompanied by DNA methylation in the male germline [42]. Maternal nutritional deficiencies can have long-term effects on the offspring, initially identified as a meta-

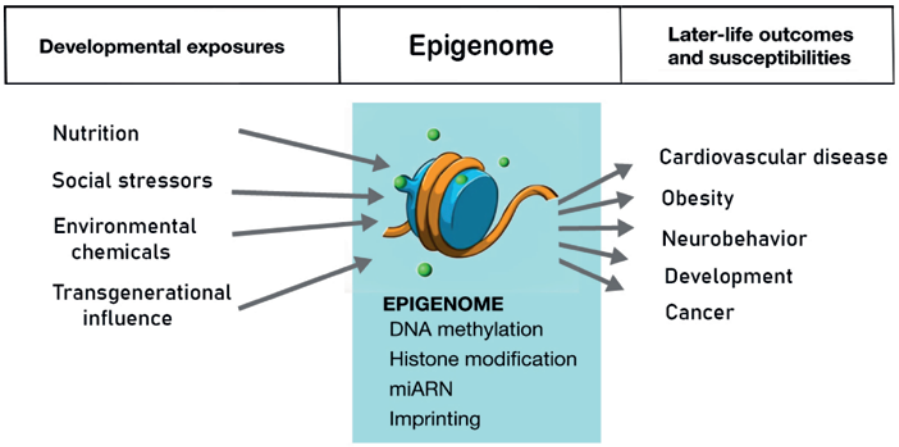

FIGURE 2. The late effects of aggressions during development mediated by epigenetic mechanisms after Boekelheide et al [9], modified

bolic program or metabolic imprinting [2,10,15,41]. Their substrate is probably epigenetic changes, as shown by studies on DNA methylation in 60 years after the period of famine in Holland in the Second World War [18]. The influence of the gestational environment on the epigenome of the offspring studied in experimental animal models showed changes that extend over 2-3 generations or even more [18,42,44]. The epigenetic transmission of trauma has been studied in Holocaust survivors, descendants of war veterans, post-traumatic stress or refugee families. A longitudinal study conducted in Norway on Vietnamese refugees highlighted a high risk of mental illness in the 3rd generation of descendants whose grandparents were diagnosed with post-traumatic stress upon arrival in Norway [43]. According to Cerutti et al [45] the DNA profiles of the child and the adult partially overlap, further studies are needed on the dynamics of DNA methylation throughout life, as it is possible that the DNA changes from the beginning period are not fixed during development. Some authors challenge the validity of the data on transgenerational epigenetic inheritance, the reported changes can be confused with genetic, ecological or cultural inheritance [46], or consider the molecular mechanisms of information transmission over the generations to be unclear [40]. The transfer of experimental data to human subjects has been contested due to the difficulties of conducting studies on several human generations, due to the possibility that DNA changes from the beginning of life are not fixed during development, or due to the involvement of other enzymatic or endocrine mechanisms.

CONCLUSIONS REMARKS

The epigenetic variations are determined by nutrition, infections, chemical noxae and stress. The programming initiated during fetal life is important in chronic pathology of adulthood. Infections, allergic diseases, malignant diseases display a significant epigenetic dimension. By acting at the beginning of the life cycle, the pediatrician can intervene in the development of these processes through prophylactic approach and epigenetic therapy, the latter being underway.

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