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EPIGENETICS AND ENVIRONMENTAL BIOETHICS

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ABSTRACT

Despite being a new area of scientific knowledge, Bioethics has developed two main references that alternate temporally: a more global Ethics, as the one defended by Potter, and the Georgetown model, which was limited to the issue of Medical Ethics, revitalizing the practical Ethics. In the last decades, a widening of Bioethics is being followed up and it came to be recognized as a new transdisciplinary discipline that is inseparable from concerns about the environment. The advancements of Genetics and the creation of Epigenetics opened new paths to Bioethics. The interaction between the environment and the structure of DNA became known, but modifications that can be passed on to the offspring without affecting the structure of the DNA were also discovered. This paper is dedicated to the analysis of the changes that can hereditarily be passed on to future generations through the interference of the environment, from Rachel Yehuda et al's recent article: Holocaust exposure induced intergenerational effects on FKBP5 methylation. Yehuda's study allowed for a glimpse over what unfolds for the future of Bioethics, its new challenges and issues and it also evidenced the fact that health and environment are in constant and inseparable connection.

Keywords: Bioethics; Genetics; Environment; Epigenetics.

EPIGENÉTICA E BIOÉTICA AMBIENTAL

RESUMO

Apesar de ser uma área recente do saber científico, a Bioética desenvolveu duas referências principais que se alternaram temporalmente: uma Ética mais global, como a defendida por Potter, e o modelo Georgetown, que se limitou à questão da Ética Médica, revitalizando a Ética prática. Nas últimas décadas, tem-se acompanhado um alargamento da Bioética, que passou a ser reconhecida como nova disciplina, transdisciplinar e indissociável das preocupações com o meio ambiente. Os avanços da Genética e a criação da Epigenética inauguraram novos caminhos à Bioética. A interação do meio ambiente com a estrutura do DNA passou a ser conhecida, mas também foram descobertas alterações que podem ser passadas à descendência, sem que tenha sido afetada a estrutura de DNA. Este trabalho dedica-se a analisar essas alterações que podem ser passadas hereditariamente a gerações futuras pela interferência do meio ambiente, a partir do recente artigo de Rachel Yehuda et al: Holocaust exposure induced intergenerational effects on FKBP5 methylation. O trabalho de Yehuda permitiu um vislumbre do que se descortina para o futuro da Bioética, seus novos desafios e problemas e, também, a comprovação de que saúde e meio ambiente estão em conexão constante e inseparável.

Palavras-chave: *Bioética; Genética; Meio Ambiente; Epigenética.*

INTRODUCTION

The development of the Health Sciences has approached, in the last decades, a more environmentally relational view. Genetics is also crossing this bridge that is being built through studies on the predisposition to diseases that are unleashed by environmental factors, as well as the structures for the interaction between health and the environment.

Knowing the human genome and the functional gene decoding seems to launch a new era of health interventions and environmental considerations.

Thus, the say that "the human being is built day by day" seems to acquire a new sense. In a first moment, the idea was that subjectivity was an ongoing construction, a product of complex morphological and physiological factors and of social relations. However, that sense is being enlarged as the human species itself seems to be a project under construction from the point of view of hereditary information. Such information, which looked like a finished map, comes up nowadays like a manuscript that may be changed at any time.

But, are the routine actions and choices of the human being able to affect them as a species from the standpoint of heredity? Thinking differently: can what you eat or how you accept or deal with daily problems affect human genotype?

This article is not a genetic research report, but it founds itself on genetic research to check the impacts produced by those individual genotype transformation conditions, having the environment and the bioethical assessment of that transformation as main factors. The objective is to show the level at which the environment directly influences human health.

All those considerations fit into the Bioethics enlargement context, just like a transdisciplinary Ethics that is able to think broadly about the phenomenon of life.

The proposed investigative procedure starts by exposing the transformation in Bioethics and its reach along the last decades. Then, considerations on human genotype from the Theory of Evolution, the conditions of heredity and of Genetics are introduced. Finally, the article *Holocaust exposure induced intergenerational effects on FKBP5 methylation* is assessed. It was released in 2015 in the *Biological Psychiatry* journal by Rachel Yehuda, a psychiatrist at *Icahn School of*

Medicine at Mount Sinai, and her team to evaluate the consequences of intergenerational effects exposed therein for health, the environment and Bioethics research.

1 A NEW HORIZON FOR BIOETHICS

The creation of the word Bioethics is quite recent and it has two main milestones: 1. the article *Bio-ethik: eine Übersicht der Ethik und der Beziehung des Menschen mit Tieren und Pflanzen* (Bio-Ethics: an overview of ethics and of the relationship between the human being, animals and plants) written by Fritz Jahr in a German magazine, Kosmos, in 1927; 2. The book *Bioethics: Bridge to the Future* written by a North-American doctor, Van Rensselaer Potter, in 1971. (NAVES; SÁ, 2013) But, it was in the 70's that the bioethical methodology and epistemology were constructed, allowing for the recognition of its autonomy in the following decades.

Born as Ethics of Life, with environmental and human health concerns, Bioethics, especially in the 70's and 80's, moved away from its ecological matrix and reinforced its concerns with the progress of Medical Science. That distance was created by adopting a new posture that Reich (1995) calls "Georgetown model" for Bioethics – once it was developed at the Georgetown University (USA), especially by André Hellegers, who revitalizes the study of Medical Ethics.

> The Georgetown model introduced a notion of bioethics that would deal with concrete medical dilemmas restricted to three issue-areas: (1) the rights and duties of patients and health professionals; (2) the rights and duties of research subjects and researchers; and (3) the formulation of public policy guidelines for clinical care and biomedical research. (REICH, 1995, p. 20)

The Georgetown model opposed the previous view, leveraged by Potter, that saw Bioethics as a new discipline with globalizing aspirations, capable of connecting Ethics and Science, while that one approached it as an old discipline, applied Ethics, getting back to the solution of concrete moral problems in the biomedical field. The perspective of the applied Ethics was different from the ancient Hippocratic tradition once it allowed analysts, laymen, to take part in the medical practices and decisions.

The *Kennedy Institute for Study of Human Reproduction and*

Bioethics was founded in 1971 at the Georgetown University, opening the way for theologians and philosophers to work. As José Luiz Telles de Almeida tells us:

> The bioethicists undertook the task of displacing medical ethics, essentially deontological and based on the millenary Hippocratic tradition, to the secular field of the conflicts existing in democratic and plural societies. That represented an urgent but difficult task, once the ethical dilemmas asked for immediate responses and the medical ethics, in the beginning of the 70's, was not a truly disciplinary field, but "a mixture of religion, curious ideas, exhortative speeches, legal precedents, several traditions, life philosophies, a miscellanea of moral rules and epithets" (Clouser, 1993: S10). (ALMEIDA, 1999, p. 54)

In 1982, Toulmin publishes an article that instigates the assessment of the change that Bioethics is causing in sciences and in Ethics itself. In the article, titled *How medicine saved the life of ethics*, Toulmin argues that Ethics had been changed into an abstract theory, far from pragmatic problems (metaethics). According to him, the moral dilemmas faced by doctors relocated the Ethics, forcing it to handle particular cases and returning to it human seriousness and relevance. (TOULMIN, 1982)

It is within this context of going back to pragmaticity and of revitalization of applied Ethics that the bioethical principialism appears, waiving pure ethical theorization and erecting normative wordings with a practical and generalist bias only related to biomedicine issues.

This is not the right place to evaluate the currents of Bioethics. However, it is important to highlight that principialism has opponents, but it was highly important in the process of affirming Bioethics. On the other hand, the broader notion of health was already requiring a more encompassing posture from Bioethics.

In 1978, the World Health Organization prepared a conference in Alma-Ata, Kazakhstan, whose final document highlights the multifactorial characteristics of health:

> I – The conference strongly reaffirms that health, which is a status of complete physical, mental and social wellness, and not simply the absence of diseases and illnesses, is a fundamental human right, and the consecution of the highest level possible of health is the most important world social target, whose achievement requires the action of several other social and economic sectors in addition to the

> health sector. (WHO, 1978, p. 1)

The first step had been taken towards the recognition of the links between health and external conditions. As of the 90's, the return to ecological concerns brought Bioethics back to the intersection with the environment.

Anyway, Bioethics was born transdisciplinary, went through a stage of epistemological subsumption to Moral Philosophy, with monolithic matrixes, and now follows the long and difficult path of transdisciplinarity. It is necessary to approach the problems in all their nuances, perspectives and consequences, but from there to effective actions, there is a long gap to be overcome.

Potter's objective to build an Ethics of survival has also been gaining strength with the consideration of future generations. However, what for some seems to be an assessment of environmental moral dilemmas, is, for Bioethics, the analysis of issues with an economic, social, environmental and health basis.

The development of biotechnology and the new findings of Genetics have been feeding that new broth with multiple ingredients.

With the latest studies of Ecogenetics and Epigenetics, susceptibilities and predispositions related to genes and their mutations when in contact with harmful environmental agents are defined. Thus, the relationship between health and environment exposes the location of the human being inside the environment and not as a mere external observer. To understand the human genome and its changing mechanisms becomes the recognition of the species' genetic assets as a legal good and a target of moral deliberations.

It is a new path once the focus is not only the changes deliberately made by the human being to their genetic material through genetic manipulation and therapy. A field is opened for the analysis of the mechanisms that result in genetic changes, or simply changes that are hereditarily transferable due to the interaction with the environment, social-cultural habits included.

One may ask: What is the influence of eating habits on the future generations? Can the high level of stress experienced in contemporary societies worsen mental and degenerative diseases for future generations? And what is our responsibility towards those future generations?

Bioethics recognizes the need to change and enlarge Ethics so that it can be a suitable instrument to evaluate behaviors and actors that are

unknown to the classic theory, and also to act as an instrument to gather knowledge in the assessment of moral dilemma regarding all kinds of life and the continuity of that same life.

Such redimensioning is also highlighted by the progresses of Genetics that require answers the traditional Ethics is not able to give, besides exposing the issue of future generations through heredity.

Ecogenetics is one of those subareas that expose the strong interaction between genome and environment. It is a branch of Genetics that is in charge of analyzing individual genetic responses that the organisms provide to environmental agents.

> By means of Ecogenetics, it was possible to prove that individuals respond differently to environmental expositions and the fact that a certain person has a specific gene that makes him/her more susceptible to a certain disease is not enough to lead to the disease, for itself. On the contrary, the influence of the environment may be a decisive factor that entails or not the development of the pathology. (RAMOS, 2015, p. 42)

Beyond Ecogenetics, the mechanisms that cause transformations that are going to be hereditarily transmitted, but that are not made through changes to the DNA structure, are studied nowadays. Understanding that instrument opens a new field to Bioethics.

In order to understand that mechanism and the importance of environmental factors in its functioning, the Theory of the Evolution is going to be approached as an introduction, as well as the development of human Genetics.

2 CONSIDERATIONS ON THE THEORY OF EVOLUTION, HEREDITY AND GENETICS

In 1859, Charles Robert Darwin (1809-1882) published *On the Origin of Species*. The influence of that text can be measured through the importance it had for the later humanity. Its origin results from the trip Darwin took as a naturalist in the now famous ship Beagle, between 1832 and 1837. In that work, Darwin proposes the famous theory of the evolution of species, mainly through natural selection:

> I am fully convinced that species are not immutable; but that those belonging to what

> are called the same genera are lineal descendants of some other and generally extinct species, in the same manner as acknowledged varieties of any one species are the descendants of that species. Furthermore, I am convinced that Natural Selection has been the main but not exclusive means of modification. (DARWIN, 1861, p. 13).

According to Mark Ridley, a zoologist at Oxford:

> Evolution means change, change in the form and behavior of organisms between generations. The forms of organisms, at all levels, from DNA sequences to the microscopic morphology and social behavior, can be changed from those of their ancestors during evolution (RIDLEY, 2006, p. 20).

Darwin's thesis was that the characteristics could be transmitted through heredity. It was noticed that albinism and skin problems remained in certain families for many generations. Thus, it was concluded that:

> If strange and rare deviations of structure are truly inherited, less strange and commoner deviations may be freely admitted to be inheritable. Perhaps the correct way of viewing the whole subject would be to look at the inheritance of every character whatever as the rule, and non-inheritance as the anomaly. (DARWIN, 1861, p. 19).

Still not aware of genetics, Darwin had no conditions to satisfactorily answer about heredity, but he raised his hypothesis:

> The laws governing inheritance are quite unknown no one can say why a peculiarity in different individuals of the same species, or in individuals of different species, is sometimes inherited and sometimes not so (DARWIN, 1861, p. 19).

Anyway, heredity would depend on the notion of natural selection[1], which, in turn, would be fundamental to explain the theory of evolution, which can be illustrated by human hands (domestication), but that would take place slowly in nature. In the words of Darwin: "This preservation of favourable variations and the rejection of injurious variations, I call Natural Selection". (DARWIN, 1861, p. 78). Or, metaphorically, he says that natural selection "is daily and hourly scrutinizing, throughout the world, every variation, even the slightest; rejecting that which is bad, preserving

1 About the relationship between natural selection and heredity DARWIN, 1861, p. 90.

and adding up all that is good; silently and insensibly working, whenever and wherever opportunity offers, at the improvement of each organic being in relation to its organic and inorganic conditions of life" (DARWIN, 1861, p. 80).

On natural selection, Ridley explains that "Natural selection can not only produce evolutionary change, it can also cause a population to stay constant. If the environment is constant and no superior form arises in the population, natural selection will keep the population the way it is" (RIDLEY, 2006, p. 105). Natural selection can also maintain a population away from variations if there are no significant changes to the environment.

Darwin's doubts about the ability to transmit factors between individuals in the same species are going to be answered by another great name in the history of science: the Augustinian monk Gregor Johann Mendel (1822-1884). On February 8 and March 8, 1865, at the Natural History Society of Brünn[2], a former city in the Austro-Hungarian Empire, Mendel presented the text *Versuche über Plflanzenhybriden* (Experiments on Plant Hybridization). As Mendel himself says, the experiment consisted in:

> Experience of artificial fertilization, such as is effected with ornamental plants in order to obtain new variations in color, has led to the experiments which will here be discussed. The striking regularity with which the same hybrid forms always reappeared whenever fertilization took place between the same species induced further experiments to be undertaken, the object of which was to follow up the developments of the hybrids in their progeny. (MENDEL, 2015, p. 1).

Through the analysis of plants with different colors (peas), Mendel noticed, by breeding several plants, how the characteristics are transmitted to the later generations.

> Those who survey the work done in this department will arrive at the conviction that among all the numerous experiments made, not one has been carried out to such an extent and in such a way as to make it possible to determine the number of different forms under which the offspring of the hybrids appear, or to arrange these forms with certainty according to their separate generations, or definitely to ascertain their statistical relations. (MENDEL, 2015, p. 2).

2 The city is now called Brno and it is located in the Czech Republic

Mendel calls the attention to the duration of the experiments, later he is saying they lasted eight years, which allowed for counting offspring, classifying them along generations and including them into the statistics.

Mendel's research used the garden pea, *Pisum sativum*. In the analysis, he checked the colors of the seed (green and yellow), of the pod (green and yellow) and the flower (purple and white), the forms of the seed (smooth/round and wrinkled/irregular) and the pod (inflated and constricted), the length of the stem (tall, i.e., between 182 and 213 cm, and dwarf, i.e., between 23 and 46 cm) and the position of the flowers (axial, i.e., distributed along the stem, and terminal, i.e., on the upper part of the stem)[3].

In the first crossbreeding (F1)[4], which Mendel called hybrid, the researcher crossed different characteristics. Among the resulting characteristics of this first relation, some are going to be called "dominant" (entirely transmitted in the first crossbreeding) and others are going to be "recessive" (they disappear in the first crossbreeding, but come back along the generations): "Henceforth in this paper those characters which are transmitted entire, or almost unchanged in the hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the dominant, and those which become latent in the process recessive". (MENDEL, 2015, p. 8). For example, in what regards colors, in the first crossbreeding, all the peas from the relation were yellow, causing yellow to be called dominant and green, recessive.

With the plants from the first crossbreeding, from which the results were only dominant characteristics, Mendel had another crossbreeding (F2), amazingly obtaining some plants with recessive characteristics. He called this stage "the first generation of the hybrids". The proportion dominant-recessive found by Mendel in that crossbreeding was an average of 3:1[5], that is, for example, regarding pea colors, for each three yellow peas, there was a green pea.

In the second crossbreeding generation, Mendel obtains a proportion of 2:1:1[6]. He notices that for every two hybrid results (green-yellow), there is one dominant and one recessive: "it is now clear that the hybrids form seeds having one or other of the two differentiating

3 Cf. Mendel, 2015, p. 04-05.

4 F1, F2 and F3 are used by Mendel to refer to the kind of crossing.

5 The results obtained by the monk were described in detail in Mendel, 2015, p. 08-11.

6 Such result can be seen in Mendel, 2015, p. 11-13.

characters, and of these one–half develop again the hybrid form, while the other half yield plants which remain constant and receive the dominant or the recessive characters in equal numbers." (MENDEL, 2015, p. 13).

From such conclusions, Mendel uses letters to illustrate his results. For example, for each four peas, one is going to be dominant, represented by "A", two are going to be hybrid, represented by "Aa", and one is going to be recessive, represented by "a". The next step Mendel took was to observe two characteristics (for example, form and color of the seed) at the same time, which allowed him to draw other statistic conclusions.

However, Mendel's first observation already contained the basis for the creation of genetics. According to Griffiths et al, reinterpreting Mendel at the light of contemporary genetics:

> 1. An hereditary factor called **gene** was necessary to produce pea color.
> 2. Each plant has a pair of that kind of gene.
> 3. Gene exists in two forms called **alleles**. If the gene is phonetically called "wye", thus the two alleles can be represented by Y (representing the yellow phenotype) and y (representing the green phenotype).
> 4. A plant can be Y/Y, y/y or Y/y. The bar shows that the alleles are in a pair.
> 5. In the plant Y/y, the Y allele dominates and, thus, the phenotype is going to be yellow. Thereby, the phenotype of the Y/y plant defines the Y allele as **dominant** and the y allele as **recessive**.
> 6. In the meiosis, the members of a pair of genes equally separate into oocyte and spermatozoa. That equal separation got known as **Mendel's First Law** or as **law of equal segregation**.
> 7. Thus, one only gamete contains just one member of each pair.
> 8. In fertilization, the gametes randomly merge, regardless which allele it brings (emphasis in the original). (GRIFFITHS et al, 2009, p. 33-34).

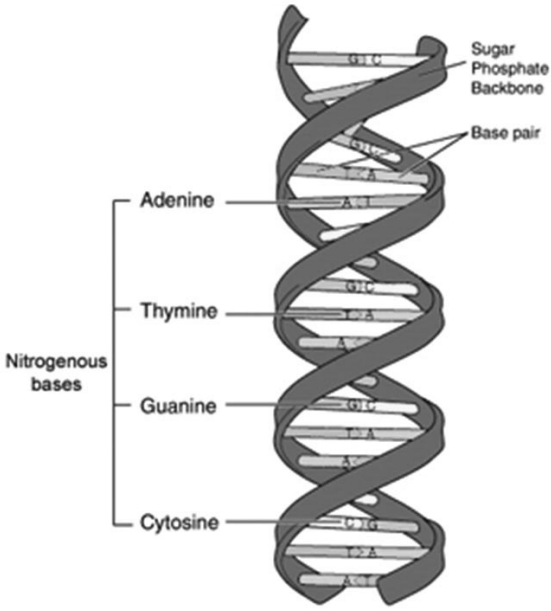
Although he is considered the father of genetics, Mendel's findings were unknown for some decades. The Austrian monk was not aware of the physical structure for the transmission of hereditary data. "The basic elements of the information system inherited nowadays are called **genes**, a term that was introduced in 1909 by Wilhelm Johannsen, who investigated heritage in beans" (emphasis in the original). (GRIFFITHS et al, 2009, p. 2). Along the end of the 19th century and the first half of the 20th century, research on heredity was carried out, but the revolution is taking place with the discovery of the chemical structure of the genetic material. "The

accumulation of evidence that started in the 1920's led to the conclusion that the DNA is the genetic material." (GRIFFITHS et al, 2009, p. 3).

By the discovery of the DNA (deoxyribonucleic acid) structure, the history of genetics was marked by the following moments: 1. hereditary factors were discovered by Mendel, but their physical structure was unknown; 2. the gene (protein) was proposed; 3. the genes are carried in chromosomes; 4. chromosomes consist in DNA and protein; 5. DNA is the genetic material. (GRIFFITHS et al, 2009).

The year of 1953 is the revolutionary moment in which the North American geneticist James Watson and the British physician Francis Crick discovered the structure of DNA:

> They proposed a definition for gene in chemical terms and, by doing that, they opened the path for the understanding of genic action and heredity at the molecular level [...]. Watson and Crick concluded that the DNA is a double helix consisting of nucleotide chromatids attached to one another. (GRIFFITHS et al, 2009, 225-226).



DNA Structure – Source: www2.le.ac.uk/departments/genetics/vgec/highereducation/topics/dnageneschromosomes

It is possible to notice from the drawing above that the chemical substance in the DNA consists in phosphate, sugar (deoxyribose) and four nitrogenous bases: adenine (A), guanine (G), cytosine (C) and thymine (T). The chains (double helixes) are called filaments and they are connected by a pair of bases (A with T and G with C).

Such structure allowed understanding over the following requirements of heredity:

> 1. The double helical structure suggests how the genetic material can define the structure of proteins. The sequence of nucleotide pairs in the DNA may define the sequence of amino acids in the protein specified by that gene. In other words, some kind of genetic code can write information in the DNA such as a sequence of nucleotides and, then, translate it into a different language of a sequence of amino acids in the protein. [...].
> 2. If the sequence of bases in the DNA specifies the sequence of amino acids, then it is possible to have a mutation due to the replacement of a kind of basis for another one in one or more positions [...].
> 3. As Watson and Crick said in the conclusion of their 1953 publication in *Nature*, when they reported the double-helix structure of the DNA: 'It has not escaped our notice (12) that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material'. (GRIFFITHS et al, 2009, 234).

Genes and, consequently, DNA are going to be the means by which hereditary characteristics are going to be transferred to individuals and later generations. However, some recent theories and research have made the supposition that the DNA may be influenced by the environment, allowing for some transformation, not to its structure. Those changes, which are going to be transmitted to later generations, are going to be called epigenetic mechanisms.

In the words of Michael K. Skinner, environmental Epigenetics may be described as follows:

> Environmental epigenetics therefore provides a molecular mechanism for the fetal basis of adult-onset disease, and will be crucial to a full understanding of disease aetiology. It should be noted, however, that the impact of epigenetic mechanisms on basic biological processes, developmental biology, disease aetiology and

> evolutionary biology does not negate the importance of genetics in these processes. The interaction of epigenetic and genetic molecular events provides a more-powerful set of tools for the regulation of these processes. (SKINNER, 2011, p. 622)

The Epigenetic studies may contribute for the ethical and legal debate regarding the environmental care from the current generations to the future ones.

3 STUDY ON THE INTERGENERATIONAL EFFECTS INVOLVING JEWS FROM THE SECOND WORLD WAR

On August 2015, an important article titled *Holocaust exposure induced intergenerational effects on FKBP5 methylation* was published in the *Biological Psychiatry*. It resulted from a research led by Rachel Yehuda from the *Icahn School of Medicine at Mount Sinai* in New York.

The researches on the epigenetic mechanisms in the intergenerational transmission on the effects of stress have not been proved in human beings, but in animals. The article tried to demonstrate that stress can be transmitted to other generations in humans.

> Parental trauma exposure is associated with greater risk for PTSD [Post Traumatic Stress Disorder], mood, and anxiety disorders in offspring. Biological alterations associated with PTSD, and/or other stress related disorders have also been observed in offspring of trauma survivors who do not themselves report trauma exposure or psychiatric disorder. Animal models have demonstrated that stress-exposure can result in epigenetic alterations in the next generation, and such mechanisms have been hypothesized to underpin vulnerability to symptoms in offspring of trauma survivors (YEHUDA et al, 2015, p. 3)

The scientific bibliography has detected that offspring of parents who were exposed to trauma are subject to Epigenetic alterations. According to the authors, there are significant signs that those alterations result in different kinds of disorders in offspring:

> Enduring behavioral responses to stress and epigenetic alterations in adult offspring have been demonstrated to be mediated by changes in gametes, *in utero* effects variations in early postnatal care and/or other early life experiences that are influenced by parental exposure. Converging data indicate that some findings in

> offspring may represent a biological accommodation to either the parental exposure, or its biobehavioral consequences. (YEHUDA et al, 2015, p. 3).

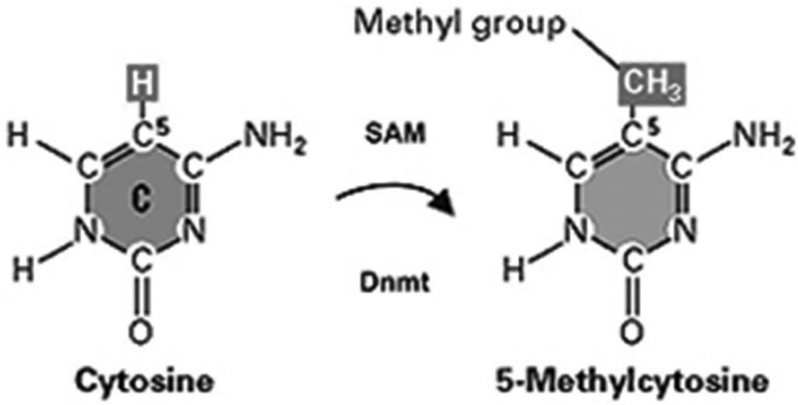
One of the great problems in the scientific literature is the fact that researchers have trouble in distinguishing what factors result from Epigenetic alterations and what factors result from childhood trauma or from life. Besides, there are phenotypic changes in adults that manifest differently in offspring. To deal with such problems, Yehuda et al chose to:

> Thus, we investigated epigenetic changes in FKBP5 methylation in Holocaust survivors, offspring and demographically–matched Jewish parent-offspring pairs from peripheral blood samples to determine whether Holocaust exposure and/or PTSD symptoms, and offspring's own experience were associated with changes in FKBP5 methylation in the Holocaust offspring. (YEHUDA et al, 2015, p. 4).

The investigation encompassed Holocaust survivors and their first generation offspring. Material was collected and certain symptoms were observed. The research focused on FKBP5, a GR – *glucocorticoid receptor* regulator that is associated to PTSD – *post-traumatic stress disorder* and that generates intergenerational effects. FKBP5 has been seen in traumas and depressions (YEHUDA et al, 2015). FKBP5 is a protein encoder gene:

> Proteins are the main determiners of the biological form and function. Those molecules influence a lot the shape, color, size, behavior and physiology of the organisms. [...] A protein is a polymer consisting of monomers called amino acids. In other words, a protein is a chain of amino acids. (GRIFFITHS et al, 2009, p. 277).

DNA methylation is the result of the enzymatic addition of methyl groups to the position of the carbon 5 of a cytosine and they can pass from one cellular generation to the other: "such inheritable alteration, in which the DNA sequence itself is not changed, is called Epigenetic heritage and the alterations (including both the DNA methylation and histone changes) are called Epigenetic marks". (GRIFFITHS et al, 2009, p. 344).



DNA Methylation – source: https://www.premedhq.com/dna-methylation

The research verified DNA methylation in holocaust survivals comparing to a group of individuals who had never had that experience. Then, the same methylation was looked for in the first offspring of holocaust to prove transmission between generations.

The research considered that Holocaust survivors were the ones locked in Nazi concentration camps and who had been tortured or seen torture, in addition to those who had to escape or hide during the war. The control group consisted of those who did not live in Europe during the Second War. Offspring, in addition to being biological children, were those raised by their parents. Those who had serious diseases, psychosis, used steroids or were chemically dependent were excluded from the research. (YEHUDA et al, 2015).

The study concluded that the same methylation changes in the FKBP5 gene happened to both Holocaust survivors and their offspring. That would be the result of Epigenetic changes.

> The main finding in this study is that Holocaust survivors and their offspring have methylation changes on the same site in a functional intronic region of the FKBP5 gene, a GR binding sequence in intron 7, but in the opposite direction. To our knowledge, these results provide the first demonstration of transmission of pre-conception stress effects resulting in epigenetic changes in both exposed parents and their offspring in adult humans. Bin 3/site 6 methylation was not associated with

> the FKBP5 risk-allele, and could not be attributed to the offspring's own trauma exposure, their own psychopathology, or other examined characteristics that might independently affect methylation of this gene. Yet, it could be attributed to Holocaust exposure in the F0. (YEHUDA et al, 2015, p. 13).

Yehuda et al suggest that other studies should be carried out with trauma survivors who were not pregnant yet and with people who were pregnant to check the causes of Epigenetic influences. They also suggest that the research is repeated with other populations that were subject to severe trauma. In order to avoid the social influence in the transmission of traumas: "It is also necessary to investigate multiple generations to differentiate among exposure effects, epigenetic inheritance and social transmission. Animal models can provide further mechanistic understanding of how extreme stress effects mediate changes in offspring." (YEHUDA et al, 2015, p. 13-14).

Even though the research had a limited universe, "a significant effect of severe parental trauma was observed in both generations at the same site of a transcriptionally relevant region of a stress-related gene". (YEHUDA et al, 2015, p. 14). The results of the research indicate the importance to check parents' experiences can play a fundamental role influencing their offspring. "In summary our data support an intergenerational epigenetic priming of the physiological response to stress in offspring of highly traumatized individuals. These changes may contribute to the increased risk for psychopathology in the F1 generation". (YEHUDA et al, 2015, p. 17).

The study ends up by suggesting that the researches should be deepened, besides saying that finding those Epigenetic marks can contribute for the prevention of problems related to intergenerational sequels.

> Future studies should focus on assessing the effects of trauma at various developmental stages, as well as potential differences in maternal and paternal effects. Additionally, the mechanism of intergenerational transmission of trauma and functional importance of site-specificity remain to be explored. Early detection of such epigenetic marks may advance the development of preventive strategies to address the intergenerational sequelae of exposure to trauma. (YEHUDA et al, 2015, p. 17).

4 SOME CONCLUSIONS ABOUT THE ARTICLE *HOLOCAUST EXPOSURE INDUCED INTERGENERATIONAL EFFECTS ON*

FKBP5 METHYLATION

The article *Holocaust exposure induced intergenerational effects on FKBP5 methylation* by Yehuda et al concludes that Epigenetic changes derived from traumas experienced by Holocaust survivors can be passed on to their offspring. That means that experiences suffered by one generation can affect the future generations.

The research illustrates how traumas in human beings can be transmitted to offspring through the Epigenetic heritage and not only through the social context. That would corroborate the notion that the environment is capable of, besides affecting human beings' own genes, affecting their offspring's genes. Thus, as holocaust survivors are traumatized and that trauma is associated to a genetic marker, the same marker was found in their offspring and it also resulted in traumatized individuals.

Although genes hold biological information that is transmitted to children and other descendants, one can notice that genes are "transformed" by the environment, which generates epigenetic markers in the genes that do not change the structure of the DNA, but that have the ability to change genetic characteristics. In the case herein, the ability to trauma is not originally in the DNA of survivors or their children, but it was associated to the marker that was connected to the DNA, which in survivors was connected to trauma experienced and, in their descendants, originated from genetic transmission.

The research detected the same Epigenetic marker in the Holocaust survivors and their children, which has not been detected in those who have not suffered the trauma of the Second World War. Then, the transmission of the markers to the future generations would be a demonstration of how the environmental transformation of a current generation deeply interferes in the health of offspring.

However, science still has a long path ahead. It is yet not clear enough how markers are transmitted between generations and why some markers are passed on and others are not, but the research analyzed is strong evidence that an environmental experience in one generation is able to affect the behavior of the following generation.

Thus, Bioethics transforms itself once again in order to assess the interventions that, deliberately or not, are produced in future generations by Epigenetics' mechanisms. One can even speculate that such Epigenetic transformations affect not only human beings, but also a wide range of

living beings whose behavior is changed and hereditarily passed on to the offspring due to the interaction with human beings. There is still a lot to research and to understand, but it is already possible to notice that human responsibility over the environment and over living beings, may they be genetically similar or not, is stretching.

It is also not possible to accept a restrictive Bioethics that only has biomedical assumptions, as if Medicine nowadays was able to do without transdisciplinarity to accomplish its main functions. The fragmentation of the medical knowledge shows its insufficiency and the human being's deliberations get a unique reach through Epigenetics.

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