MECHANISMS OF DARWINIAN MEDICINE IN CHRONIC NONCOMMUNICABLE DISEASES

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INTRODUCTION

Evolution through natural selection as postulated by Charles Darwin in his book “The Origin of Species” in 1859 is the basis of modern biology. Human beings are the result of a long evolutionary process and the best way to understand our capabilities and our limitations is putting them in the perspective of our evolution. Evolutionary biology should be central to understanding the causes of our health problems, but a proper application of evolutionary biology to medicine has not been reached. The process of linking medicine and evolution has been long and misunderstandings have prevailed. It was not until in 1994 Doctor Randolph M. Neese and evolutionary biologist George C. Williams, that a novel area of study known as "Darwinian Medicine" was proposed in their book “Why we get sick”.

The genetic material (genotype), the environment and interaction between both may be the cause of diseases. Illnesses can be considered as phenotypes generated by the expression of sets of genes in determined environments. The promises of the human genome studies to solve genetic origins of diseases have not been met, because there are very few diseases with a simple genetic basis. The majority of diseases involve many genes, and a complex interplay with the environment.

Many diseases can be traced to a mismatch between the environment met during early stages of development in

which many set points of regulatory pathways were determined, and the environment met in adult life. This issue might constitute a biological mechanism for Darwinian medicine. However, conditions during the adult stage also differ from those in which the organism developed or evolved. The origin of the diseases could therefore be sought in the individual strategies during the early stages of development as addressed by the "life history" theory of Ronald A. Fisher, who proposed this hypothesis in his work “The Genetical Theory of Natural Selection” in1930. The concept of "trade-off" (commitment or investment exchange), explains that there exists a limited amount of resources (energy, nutrients or time) which must be administered between different activities in the individual, determining lifespan and susceptibility to diseases. Even before a baby is born, the maternal environment is critical in terms of resources for fetal development and the expression of genes.

Diseases are also generated by a poor adaptation to current environmental conditions when compared to those in which the organisms evolved. The metabolic syndrome and obesity could be the result of our feeding habits and sedentary lifestyle and hypertension could appear as a consequence of high salt ingestion and bipedalism. Aging which also appeared late in the evolution of the human species has brought with it an enormous amount of related chronic diseases.

In addition to misplacement of regulatory set points of functions during early development and to a poor adaptation to the current environment and lifestyle, other possible biological mechanisms participating in the appearance of diseases might be the presence atavistic genes and/or heterochrony, and pleiotropism. These mechanisms have been proposed to participate in regenerative medicine and aging by Darwinian medicine. Atavistic genes are genes that were expressed in our ancestors but have remained silent during evolution and are suddenly expressed without an apparent cause. Heterochrony is the expression of genes that cause the appearance of traits at a different timing during development and is therefore related to atavisms. Neoteny (a slower rate of somatic development) or the appearance of the capacity to reproduce while the organisms´ somatic development has not been reached could be the most well-known form of heterochrony. Pleiotropism refers to genes participating in different functions while antagonic pleiotropism refers to genes that are beneficial during certain stages of development but become detrimental in others. Mechanisms such as pleiotropism and antagonistic pleiotropism and atavistic genes or heterochrony are basic for explaining the new perspective of important aspects of biology and Darwinian medicine. Although pleiotropy in the genetic architecture of complex disease has been proposed, to date, evidence for its presence has not been systematically

evaluated despite suggestions that it could be useful. A similar situation happens with atavistic genes and heterochrony which could play an important role in diseases such as cancer.

On another hand, when the differentiation stage of certain cells or organisms does not correspond to the environment in which they finally develop and live, a predisposition to diseases exists. A difficult situation also arises to apply methodologies such as the use of stem cells for regeneration. A mismatch between the developmental stage of stem cells and the tissue in which they are implanted, that constitutes the environment to which they must adapt, is also an important issue for regenerative and Darwinian medicine. All these mechanisms applied to different pathologies shall be discussed in this book.

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PART 1

Mechanisms in Darwinian Medicine

Chapter 1
MECHANISMS OF DARWINIAN MEDICINE

Three main mechanisms have been postulated to participate in Darwinian medicine:

1) Atavistic genes
2) Heterochrony
3) Pleiotropy, antagonistic pleiotropy and ecological antagonistic pleiotropy

Atavistic Genes

The first studies of Evo-Devo identified conserved sets of toolkits common to most metazoans which include atavistic genes. Atavistic genes are fragments of DNA whose expression seemed to have disappeared from the development of the organism and that suddenly appear during the course of its life.

Atavistic traits may be a cause of diseases and an important mechanism in Darwinian medicine. Traits such as extra nipples or tails in humans, hind limbs in whales, teeth in birds, or wings in wingless stick insects remind us that certain genetic information is not completely lost but can be reactivated. Atavisms seem to violate one of the central evolutionary principles, known as the law of Dollo that states that "an organism is unable to return, even partially, to a

previous stage already realized in the ranks of its ancestors." Although it is still not clear what triggers and controls the reactivation of dormant traits, atavisms are a challenge to evolutionary biologists and geneticists.

The conservation of atavistic genes indicates their participation in essential functions in primitive organisms. They were possibly functional before the appearance of multicellular species. Some of these genes are considered to be proto-oncogenes. The return to the functionality of certain genes by defective regulation might be involved in the appearance of diseases in modern organisms. Comparative genomics and the phylogeny of basal metazoans should help identify relevant genes associated to atavisms in mammals and yield the order in which they evolved. This order might be a rough guide to reverse cancer, a disease related to atavism which develops as mutations disrupt the genes of cellular cooperation. (Davies and Lineweaver , 2011).

Atavistic genotypes have been related to deletion of HoxA and HoxB genes in some organs such as the heart. The vertebrate body plan is characterized by an increased complexity relative to that of all other chordates and large-scale gene amplifications have been associated with key morphological innovations leading to their remarkable evolutionary success. Gene duplications associated to Hox have contributed to the emergence of vertebrate-specific

innovations and the resurgence of ancestral features and with the formation of novel regulatory controls.

Heterochrony

During heterochrony, the timing of the expression of certain genes, groups of genes or traits is altered. It constitutes a mechanism by which new gene expression patterns can produce novel morphological structures or can form robust patterns that can both facilitate and resist change. Comparative developmental biology is studying regulatory regions of developmentally important genes to compare them to others and to study the different morphological structures they produce.

After the publication of Darwin's “Origin of Species” in 1859, Ernst Haeckel formulated his biogenetic law in 1872, stating that ontogeny recapitulates phylogeny. This work was a previous important attempt to make a synthesis between evolution and development that has been recently newly undertaken with Evo-Devo theories. Changes in the timing or positioning of an aspect of development in a descendant relative to an ancestor (some forms of heterochrony including acceleration of development and terminal addition of new characteristics and heterotopy) were the two evolutionary developmental mechanisms identified by Ernst Haeckel in the 1870s. Haeckel was influenced by pre-Darwinian thinkers such as Karl Ernst von Baer, who had noted that earlier

developmental stages show similarities to behaviors in children that are not seen in the adults.

The concept of heterochrony is helping the synthesis of developmental genetics with evolutionary genetics and increasing the understanding of significant evolutionary changes in multicellular organisms. More changes in timing or positioning of aspects of development have been identified since Haekel. Heterochrony includes three patterns: a) neoteny (retardation in somatic development in which an organism is capable of reproducing while still having embryonic or larval features), b) progenesis (acceleration in gonadal development), and c) direct development (acceleration in somatic development, resulting in lack of larval stages).

Mechanisms underlying heterochrony include morphogenetic clocks, heterochronic genes in *Drosophila* and *C. elegans*, temporal co-linearity in Hox gene complex in mice, and atavistic transformation induced by altered expression of Hox genes.

Heterochrony could be explained by the timing of appearance of modular structures of trait development and epigenetic interactions among modules during ontogeny which affect patterns of phenotypic and genetic variation. Genetic modules include gene networks and gene cascades that link the genotype with cellular modules that comprise germ layers, embryonic fields or cellular condensations.

Epigenetic processes such as embryonic inductions, tissue interactions and functional integration, link morphogenetic units to the phenotype.

Any genetic change in the mapping of modules reflects a change in development. Comparative studies of morphology as well as of gene regulatory networks show that the genotype-phenotype map itself evolves; however, little is known about the actual evolutionary mechanisms involved.

Pleiotropy, Antagonistic Pleiotropy and Ecological Antagonistic Pleiotropy

Pleiotropy is the property of genes to affect multiple functions or characters of an organism and it was first noticed 100 years ago when it was reported that mutations tend to affect more than one phenotypic characteristic. Pleiotropic genes underlie genetic covariance between traits, often causing evolutionary constraints. Genes vary widely in their degree of pleiotropy, but this variation is often considered as a by-product of their evolutionary history. The finding of pleiotropy has major implications for the evolution of complex organisms and the mapping of disease-causing mutations.

Whether genes become pleiotropic or specialize on a single function depends on the nature of trade-offs as gene activities contribute to different traits and on how the functionality of these traits affects fitness. When a gene product can perform well at two functions, it evolves to do so,

but it does not evolve when pleiotropy would greatly disrupt each function. Consequently, reduced pleiotropy should evolve, with genes specializing on the trait that is currently more important to fitness. Even when pleiotropy does evolve, not all genes are expected to become equally pleiotropic; genes with higher levels of expression are more likely to evolve greater pleiotropy. In many cases genes duplicate when they develop pleiotropy. Duplicates are expected to maintain a certain degree of functional redundancy, with the gene contributing more to trait functionality evolving the highest degree of pleiotropy.

Identifying pleiotropic traits and studying how genes and modules are used differently through evolution to build the past and present morphological diversity is one of the main waves of Evo-devo. The modular structure of trait development previously described as a foundation for heterochrony might be due to pleiotropic gene effects of modular units. Evo-devo might enable us to read the entire history of life on this planet and will show the mechanisms generating organic diversity.

Antagonistic pleiotropy (AP), or genetic tradeoff, is an important concept that is frequently invoked in theories of aging, cancer, genetic disease and other common phenomena important to Darwinian medicine. An adaptive change in one character can be associated with deleterious pleiotropy in others and subsequent selection to compensate

for these pleiotropic effects. The prevalence of antagonistic pleiotropy, the genes selected and to what extent and how its undesirable effects can be resolved remain unclear. Antagonistic pleiotropy could also happen at different stages in the life of an organism. A characteristic that may be beneficial during the reproductive phase could be deleterious during aging.

The concept of a Darwinian-evolutionary basis for the development of age-related diseases postulates that genetic traits that are beneficial in younger years to allow for successful reproduction may become deleterious in the elderly, when selective pressure is not effective anymore. Such diseases include atherosclerosis, benign and malignant prostate hypertrophy, Alzheimer's disease and the reciprocal relationship between cellular senescence and cancer.

Evolutionary pressures have selected for successful reproduction, making it likely that the post-reproductive physiology of an organism is an epigenetic and pleiotropic manifestation of the optimization for early fitness. Indeed, antagonistic pleiotropy, where genes enhancing early survival and function turn to be disadvantageous later in life, may play an important role in aging. Increasing evidence suggests that cellular senescence and aging of organisms are antagonistically pleiotropic manifestations of evolutionary pressures to prevent malignant transformation. In other words, the phenotypic characteristics related to aging may be

the price we pay to avoid cancer. The beneficial paradox may be that the maximum lifespan potential of humans may have been achieved, in part, due to our ability to grow old.

Early programming is a well documented process in animals, in which adverse conditions such as malnutrition, acting during the early stages of development, may permanently modify the structure and function of the organism. During gestation and lactation, tissue growth is very fast requiring cellular proliferation, migration and organization. Furthermore, during these developmental stages set- points of metabolic regulation are settled. Due to these, systems and organisms are susceptible to be modified or altered by environmental factors such as malnutrition leading to long lasting consequences. If diet is altered during gestation, the descendents will show permanent physiological and biochemical changes that may be adaptive and enhance survival and growth of the fetus but that lead to undesirable long- term costs; they may predispose to obesity or metabolic syndrome in adult life. Most models of fetal programming involve perturbations that produce low birth weight in offspring.

A similar process to antagonistic pleiotropy may happen in traits that were adaptive to certain environmental conditions in which evolution took place but become deleterious to the current modern lifestyle. These trends seem to cause a mismatch between our evolutionary design and

our nowadays conditions of life rendering us more vulnerable to diseases. Therefore, there seems to be an ecological antagonistic pleiotropic effect upon evolutionary traits that predisposes our species to many diseases that are becoming epidemics in the XXI century. Examples of mismatch of conditions in which we evolved and current conditions that have resulted in an increased risk to develop diseases are shown in Table 1.

Table 1. Actual conditions to which humans are not well adapted and disease to which we are at a higher risk of developing due to current environmental conditions.

CONDITION TO WHICH HUMANS ARE NOT WELL ADAPTED	ENVIRONMENTAL CONDITIONS TO WHICH HUMANS ADAPTED	RISK DERIVED FROM POOR ADAPTATION TO CONDITIONS	
Low grade chronic inflammation	Great infectious burden with an active immune system	Low grade systemic inflammation that leads to metabolic syndrome, diabetes, cardiovascular diseases and hypertension	
Abundant diet high in carbohydrates	Famine and necessity to store fat	Increased risk of obesity, Insulin Resistance, Metabolic Syndrome and type-2 Diabetes	
Sedentarism	High physical activity	Insulin Resistance, Obesity, Metabolic Syndrome and type-2 Diabetes	
Diet high in salt	Little salt in the diet	Hypertension	
Bipedalism	Quadruped movement	Orthostatic intolerance and hypertension	
Longevity	Shorter lifespan	Increased exposure to the above-mentioned risk factors	

The inverse process to pleiotropy in which a single trait is regulated by many genes is known as epistasis and it is a possible cause of why it is difficult to find a single gene that is responsible for many diseases.

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Chapter 2
DEVELOPMENT AND EVOLUTION IN DARWINIAN MEDICINE

Development is the process by which genotypes are transformed into phenotypes. It connects the genotypes passed from one generation to the next to the phenotypes that are made available for selection. Developmental biology has been influenced by the evolutionary concepts and a new field of research that takes into account evolutionary developmental biology has evolved named Evo-Devo. Evo-Devo seeks to understand how variations in development affect evolutionary changes and how evolution is restricted by the mechanisms of development (Figure 1). It is also involved in how developmental processes and mechanisms were modified during evolution to produce the current biodiversity. It studies how the hereditable changes in development can cause new phenotypes that can be preserved through natural selection or how the changes in such mechanisms of development could be the evolutionary origins of different phenotypes including diseases. It might, therefore, help understand mechanisms involved in Darwinian medicine.

Biological mechanisms that participate in the origin of diseases from a Darwinian medicine point of view are linked to development and evolution which are intrinsically intertwined. In other words, development and physiology

translate genetic variation into phenotypic variation. Evo-Devo constitutes a meeting point of developmental biology with evolutionary biology, medicine, and ecology. These areas interact with one another to evidence questions of developmental biology that had not received attention such as genetic assimilation and life history strategies; teratology, endocrine disruption and developmental constraints.

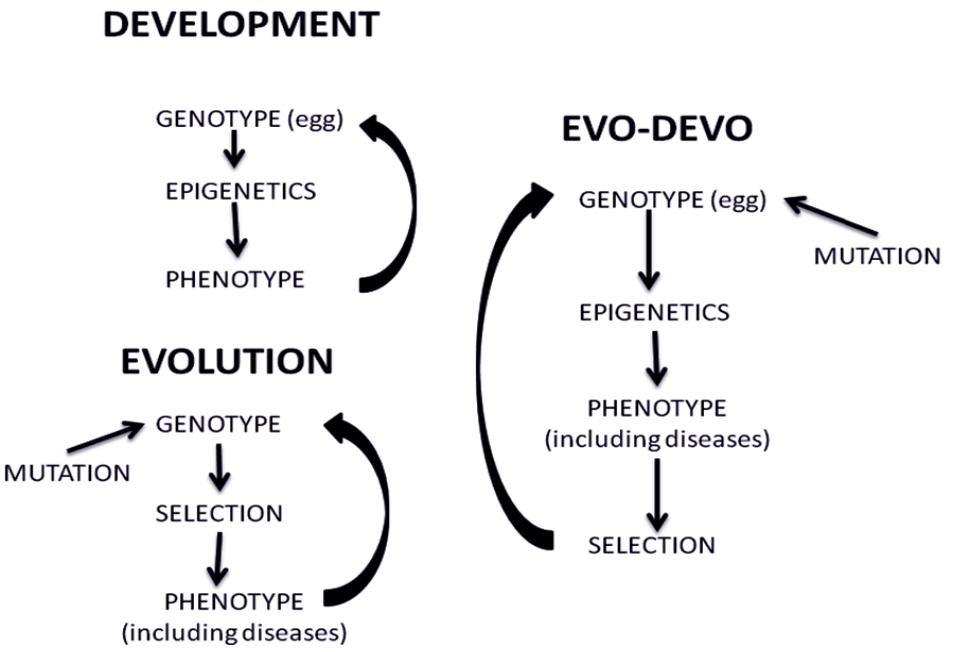

Figure 1. Synthesis of the processes in development and evolution in the new field of Evo-Devo.

Evo-Devo mechanisms include interactions between individuals of the same species, individuals of different species, and species and their biotic and/or abiotic

environment, which link ecological comunities and which also underlie interactions within embryos. There are important interactions within the developing organism, including the conditions in which development takes place. Temperature, nutrition, population density, and even infectious microorganisms can determine the sex of some animals, and morphological changes that can be brought about by predators, competitors, and even physical stress. These interactions could also establish a predisposition to develop diseases. Organisms develop a symbiosis with other organisms that can alter gene expression patterns and sometimes even modify anatomical phenotype. Ecological developmental biology is also connected to teratology since environmental effects on development are sometimes detrimental. How the environment regulates cell growth, cell division, and cell death becomes an important issue for developmental biologists, conservation biologists, and public health biologists.

An important question in evolutionary biology is what causes evolution to proceed toward certain developmental pathways rather than others, and therefore to the preservation of certain phenotypes including diseases. Whether the direction of evolution is determined by the nature of the ontogenetic process and the ways in which it can be altered by mutations in developmental genes is still under debate.

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Chapter 3

STEM CELLS AND THE EVOLVING FIELD OF DARWINIAN MEDICINE

The use of stem cells to regenerate tissues has been questioned in the light of the mechanism are involved in Darwinian medicine. The failure of improvement of tissue function after the implantation of stem cells to damaged tissues may be due to environmental antagonistic pleiotropy.

Stem Cells

Stem cells are present throughout embryonic development and in adult organs. They play a critical role during adult growth and regeneration. Basically, there are two types of stem cells: embryonic stem cells (ESCs) that can be isolated from the inner cell mass of blastocysts and adult stem cells (ASCs) that are pluripotent cells that respond to paracrine factors. ESCs and ASCs have tightly controlled proliferation, self-renewal and genomic stability. They need to maintain their own population through self-renewal and to give rise to differentiated cells which carry out most body functions and can undergo two different modes of cell division – asymmetric and symmetric. In the asymmetric division mode, one daughter cell is maintained as the stem cell and the other evolves into terminally differentiated cells. Stem cells can also divide symmetrically, leading to either two stem

cells or two differentiated cells. Symmetric divisions are required in situations such as morphogenesis and tissue injury where stem cells need to proliferate rapidly. A balance must be maintained between proliferation and differentiation to prevent malignant growth. Population level equilibrium is achieved by maintaining a stasis at the single cell level through asymmetric cell divisions.

Biological evidence for cell asymmetry is quite strong in many invertebrate systems. Studies looking at invertebrate systems, in particular *Drosophila melanogaster* and *Caenorhabditis elegans*, have found a predominance of asymmetric divisions where each stem cell division gives rise to one stem cell and one differentiated cell on average. However, homeostasis is maintained by having a subset of cells that proliferate while other stem cells are lost through differentiation. Equilibrium is reached at the population level more than at the degree of individual cell divisions if the gain and loss are balanced. In mammals in contrast to invertebrates, populations of stem cells are not maintained at an equilibrium level. This does not seem to happen in all species. The balance between cell asymmetry and population asymmetry of stem cells is still a matter for future studies.

ESCs are a part of the germline that can lead to asexual reproduction. Molecular information on the expression of germ plasm components is needed during early development of organisms which are capable of undergoing

asexual reproduction and regeneration. In sexually reproducing organisms, the germline transmits genetic material to the next generation and produce gametes. During early embryonic development, somatic cells give rise to a small population of cells known as germ cells, which eventually differentiate into mature gametes. Germ cells undergo a process of removing and resetting relevant epigenetic information, mainly by DNA demethylation. This extensive epigenetic reprogramming leads to the conversion of germ cells into immortal cells that can pass on the genome to the next generation. In the absence of germline-specific reprogramming, germ cells would preserve the old, parental epigenetic memory. The cell lineage of germ plasm component-containing cells will shed light on their position with respect to the Weismann barrier which states that there exist limits to cell division and the inclusion of the primordial stem cells as a part of the germ line, solving many controversies as originally envisaged by August Weismann.

There are some genes that act as regulators of division and differentiation of ESCs such as the piwi genes which were found in *C. teleta*. Piwi genes are co-regulators that became restricted to the germline in some taxa during the course of evolution. In *C. teleta, piwi* genes may have retained an ancestral role as genetic regulators of both somatic and germline stem cells. It is likely that *piwi* genes,

and associated stem cell co-regulators that became restricted to the germline in some taxa during the course of evolution.

ASCs retain the potential for self-renewal and differentiation into different cell types, but they have lost pluripotency as well as the capacity to form a complete new organism. They are found in most tissues and organs including the nervous system, bone marrow, epidermis, skeletal muscle, mammary gland and liver. The adult tissues have reduced stem cell function and a reduced regenerative capacity which correlates with a loss of plasticity and microvascular density. The inherent ability of cells to reprogram their fate by switching into an embryonic-like, pluripotent progenitor state is an evolutionary vestige that is mostly retained in fetal tissues and persists in a few organs of the adult body in mammals. ASCs are vital for the normal turnover of organs and they are necessary for replenishing specialized cells when they are lost after tissue damage.

In organs, ASCs are kept in specific sites where they remain in a dormant state during most of the lifetime of the host. However, when new cells are required, these tissue stem cells divide, frequently in an asymmetric way, generating another stem cell at the same time as a committed progenitor daughter cell. The progenitor cell then proliferates and produces a group of differentiated cells.

The enzyme prolyl-isomerase Pin1 regulates lineage commitment and cell differentiation of ASCs. Pin1 maintains

the balance between stem cell pluripotency, stemness and commitment by stabilizing and activating molecules controlling self-renewal and differentiation. Furthermore, Pin1 regulates cardiac hypertrophy which makes this molecule central to many of the most significant areas of myocardial signal transduction.

Modulation of bone morphogenetic protein (BMP) signaling also appears to be an important component of the postnatal stem cell niche. BMPs are members of the diverse transforming growth factor β (TGFβ) family of secreted ligands. Modulation of BMP signaling appears to be an important component of the postnatal stem cell niche. BMPs play an important role in the pleiotropic effects of postmitotic cells. This signaling may have importance for stem cell mobilization, differentiation, and cell integration/survival in reparative therapies.

Neotenic organisms that are able to reproduce while maintaining somatic “larval” characteristics, retain stemness, self-renewal, and differentiation in embryonic and many adult cell types. Therefore, they are better able to regenerate different tissues.

Mechanisms of evolutionary medicine and regeneration using stem cells

The role of stem and pluripotent cells as potential medical therapies has drawn the attention of Darwinian medicine. Stem cell- based therapies have opened exciting possibilities since they represent the basis for regenerative medicine. These cells have not yet determined their functional set points and the possibility that they may determine different set points than surrounding tissue when used in regenerative medicine may pose difficulties. There is a need for the correct use of the basic information generated from studies of embryonic development to be able to translate it into the practical needed parameters to achieve a correct tissue neo-morphogenesis. This is a challenge for developmental biology.

The mismatch between the natural environment in which stem cells develop and the environment to which they are implanted during regenerative therapies may also cause difficulties in their employment. The environment, which is continually changing during development, programs or reprograms pluripotent ASC cells. Tissue stem/progenitor cells should adapt to the organism homeostasis adjusting self renewal and differentiation when facing detrimental genetic and environmental factors to avoid aging and tumorigenesis. Apoptosis induced by DNA damage and genetic instability impairs organ function and cell cycle arrest may affect the

self-renewal of tissue stem/progenitor cells, thus altering their ability to replace damaged cells. Growth factors might become the most important signaling molecules in the next decades since adult host cells or their stem cells can respond to them. Transplanted cells and/or groups of cells can be the passive recipients of growth factors or active agents of morphogenesis.

For the correct use of ASCs by developmental biologist, it is necessary to trace their origin, to determine their phenotypic characteristics, and to investigate the molecular cues that regulate their differentiation activities. This information is crucial for the isolation and culture expansion of these cells and the formation of tissues and organs *in vitro* or *in vivo*. For example, tissue engineering of connective tissues would first require of the isolation, culture, and proper differentiation of stems cells. These cells must then be efficiently loaded and optimally harbored within a biodegradable polymeric scaffold and exposed to a bioactive milieu containing a cocktail of paracrine growth factors and/or cytokines selected for their ability to induce the desired cellular differentiation.

Candidate stem cells that can restore heart muscle and liver function have been found. Identification of molecules and reagents that influence neuronal differentiation of progenitor cells has opened the door for cell-based therapies

of Parkinson disease and the possible restoration of function across formerly severed spinal nerves.

Another important area of stem cell biology is the genetic engineering of stromal cells. Although a great deal of genetic engineering with the epithelium can be done, the same cannot be said for the stroma. This is true because of the relative paucity of organ-specific stromal promoters, but it is also due to the fact that the epithelium is relatively more accessible. This deficiency will be remedied as biologists and physicians begin to realize the opportunities these cells provide for analyzing morphogenesis and for investigating (and perhaps ameliorating) disease. From the perspective of Darwinian medicine the study of wound healing in which no scar is produced which is found in a variety of vertebrates, namely, fish, amphibians, and mammals is important since it might help reach the ultimate goal of -free human wound healing. However, despite comparative studies of adult and fetal wound healing there are still no therapies that can regenerate adult human skin.

Cloning technology may make it possible to generate multipotent or totipotent stem cells using one's own nuclei. This "therapeutic cloning" is controversial, and different nations may enact different statutes regulating it. In some instances, the plastic cells of the adult body may still be able to respond to paracrine factors without their first having to be isolated from the body.

Since extensive proliferation and differentiation of stem cells can contribute to hyper-proliferative disorders, a coordinated control of stem cell self-renewal and differentiation is fundamental for maintaining tissue and organ homeostasis. Defects in proliferation and differentiation of stem cells contribute to premature aging, to failure to repair tissue injury and to the development of cancer. An evolutionary explanation for phenotypic plasticity having potential consequences for the understanding of “cancer stem cells” is provided by the life history theory which suggests that dosing schedules might select for fast or slow life history cell phenotypes, with important clinical consequences. Fast life history organisms reproduce rapidly, whereas individuals with slow life histories invest more resources in survival and show less fecundity rates.

Detailed knowledge about the processes that regulate proliferation, self-renewal and transformation of tissue stem cells is therefore crucial to enable safe usage of these cells for stem-cell-based therapies. The tumor suppressor protein p53 is a key regulator of these processes. p53 confers protection against cancer and death by interrupting the abnormal proliferation of cells. It appears to contribute to this restraint by controlling proliferation, self renewal and differentiation of embryonic and ASCs. However, the ability to interrupt cell proliferation can be deleterious if it interferes with the proliferation of normal cells, such as stem cells, which are

needed for tissue renewal as the organism ages. A loss of regenerative capacity in these cells would be easily explained by hyperactivity of p53 at the promoters of cell cycle arrest genes, which would limit cell proliferation and the production of replacement cells.

Although there seems to be an enormous potential for the use of stem cells for regeneration and disease control, mismatch between the degrees of development of these cells and the maturation of surrounding tissue might become a challenge and further studies are needed for the use of these technologies to be a reality.

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Chapter 4

AGING AND EVOLUTIONARY MEDICINE MECHANISMS

Lifespan has increased in recent times, and the decrease in physiological capacity and the reduced ability to respond to environmental stresses leads to increased vulnerability to diseases and their consequences at this stage of life. Consequently, mortality due to all causes increases exponentially with aging.

Aging is a complex process and its causes remain unknown. Aging changes are present from the molecular to the organism level. Since the mechanisms of aging could vary between different organisms, tissues, and cells, a unifying theory has not been proposed. Theories of aging can be divided into stochastic and developmental-genetic. These are not exclusive.

Aging is associated with immunological changes, denominated immunosenescence. These immunological changes resemble those observed following chronic stress or glucocorticoid treatment. The chronic inflammation state accompanied by other factors that include increased oxidative stress, a decrease in ovarian function, a decrease in stress-induced glucocorticoid sensitivity of pro-inflammatory cytokine production in men, and an increased incidence of

asymptomatic bacteriuria. Healthy elders are more stressed and show activation of the hypothalamus-hipophysis-adrenal axis, when compared with young subjects.

Evolutionary theories of aging open new opportunities for further research and suggest testable predictions, but they have also imposed limitations on aging studies. The evolutionary theory of senescence is based on the principles proposed by Williams in 1957, and its construction is based upon ideas first suggested Medawar, Haldane and others. These ideas explain how something as apparently negative as senescence could have been benefic in evolution, particularly when most animals in the wild do not reach senescence. At this time, the evolutionary theories of aging are not completed theories, but constitute a set of ideas that require further elaboration and validation. At least the next five major evolutionary theories of aging have been proposed:

The theory of programmed death

This theory was suggested by August Weismann and could be caused by atavistic genes. The senescence effect of genes accumulates in a random, non-directed fashion in various species over evolutionary time. Some authors have attributed aging to atavistic genes. Aging genes were present in eukaryotic cells since or shortly after the emergence of eukaryotes from their prokaryotic ancestors and have been conserved ever since. Complicated explanations of how so-

called "death genes" may have evolved in eukaryotes are thus not required. These genes could be considered as atavistic genes. Some authors have proposed that the evolutionary theory of senescence should be based mainly on the evolutionary principles that have been experimentally validated such as the atavistic genes, and that the proposal of antagonistic pleiotropy which has not been experimentally validated could be dropped from the explanations of senescence from an evolutionary viewpoint.

The mutation accumulation theory of aging

This theory was suggested by Peter Medawar. Higher organisms depend on the regenerative ability of tissue stem cells to maintain tissue integrity throughout adulthood. The failure of stem cells to replace worn out, dead, or damaged cells is seen as one mechanism that limits life span. In these organisms, tumor suppressors such as p53 are central participants in the control of longevity because they regulate stem cell proliferation. Several recent reports have identified p53 as a longevity gene in organisms such as *Caenorhabditis elegans* and *Drosophila melanogaster,* which lack proliferative stem cells in all but the germline and have relatively short life spans. This has forced the reevaluation of the role of p53 in the control of life span. p53 might regulate longevity in both long- and short-lived species by controlling the activity of insulin-like molecules that operate in proliferating and non-

proliferating compartments of adult somatic tissues. Loss of p53 has life span extending effects possibly by facilitating the response to severe nutrient deprivation that allows metabolically active cells to survive periods of starvation. Paradoxically, the loss of p53 function in these cells would compromise life span.

The antagonistic pleiotropy theory of aging

George Williams proposed that the genes responsible for the negative effects of senescence were selected during evolution by a process called antagonistic pleiotropy. Genes could be actively selected by their reproductive advantage early in life, by improving fitness and by contributing to structure aging through a program that optimizes the energy availability in the post reproductive state. Thus, aging is not a selected trait, and only the consequence of genes fixed in evolution by their reproductive advantage early in life, but with harmful effects in the post reproductive period. Antagonistic pleiotropy theory might also be applied to the hypothesis of aging as a remodeling process dominated by the continuous capability to respond to inflammatory stimuli. It proposes that the presence of gene variants favorable for survival at young age and/or in an ancestral environment full of inflammatory stimuli became detrimental at the old post-reproductive age in an optimized hygienized environment. The negative selection against these harmful effects failed because, the force of

natural selection declines with age. The disposable soma theory is a special case of the antagonistic pleiotropy theory, developed by Tom Kirkwood and Robin Holliday.

p53 is a candidate molecule to be considered as an antagonistic pleiotropic gene. Programs driven by p53 such as apoptosis and cellular senescence, protect organisms from cancer early in life, but promote the aging phenotype in older individuals. Super-p53 mice have increased tumor suppression without deleterious consequences on life span and may live longer than wild type mice. The function of p53 in tumor suppression involves the trans-activation or trans-repression of a large number of genes involved in cell cycle regulation and apoptosis, such as the cyclin-dependent kinase (cdk) inhibitor p21.The p21 promoter is regulated by p53 and the insulin-like growth factor receptor (IGF-1R). However, high levels of p21 can also inhibit the proliferation of normal cells such as lymphocytes. Therefore, increased p21 could have deleterious effects on life span by blocking stem cell proliferation and preventing the generation of replacement cells needed to maintain tissue homeostasis. This could be an example of antagonistic pleiotropy caused by p53. Elevated levels of p21 block the proliferation of both tumor cells and normal tissue stem cells. Therefore, there is a rationale for the co-evolution of cancer resistance and longevity. However, excess p53 is linked to loss of trans-repression, increased insulin/IGF signaling, and accelerated aging. This may

happen when p53 cannot interact normally with transcription complexes assembled on promoters of its target genes.

The harmful effects of pleiotropic genes often do not become apparent until after reproduction, and as a result they cannot be eliminated by natural selection.

Calorie intake associated to aging

Another theory of aging associates aging with calorie intake and proposes that calorie restriction might increase lifespan. Dietary restriction promotes the preservation and generation of neurons via induction of neurotrophic factors and therefore nutrition and cognition are intimately linked and promote longevity. Dietary restriction results in lengthened lifespan, delayed sexual maturation, depressed growth and increased encephalization as a consequence of body mass reduction and brain mass maintenance. Longevity and depressed somatic and sexual development could explain the expansion of the human brain and were adaptations possibly selected during the Plio-Pleistocene period during which many environmental changes happened, which elicited changes in the human diet.

Transgenic mice over-expressing the histone deacetylase SIRT1 resemble mice that undergo a calorie restriction regimen. The manipulation of SIRT1 levels in mice increases longevity. SIRT1 activators can lessen the detrimental effects on life span caused by the consumption of

excess fat or the so-called “western diet”. Therefore, increased SIRT1 is associated with longer life span and decreased SIRT1 with shorter life span. *In vivo*, the level of SIRT1 in organs with high mitotic activity, such as the testis and thymus, declines with age. In mice exhibiting accelerated aging this decrease takes place more rapidly, and in long-lived mice it happens more slowly than in mice that age normally.

Increased longevity is also associated with decreased IGF-1R (in worms, flies, and mice). However, tumor suppression by p53 is enhanced by a decrease in SIRT1 and a lowering of IGF-1R. This means that changes that decrease SIRT1 (and increase p53 acetylation) decrease the risk of developing tumors but increase the risk of aging. The deleterious effects of p53 on aging are not only attributable to the p53 gene but involve at least another gene such as SIRT1 that modifies the effects on p53 activity.

Life history and aging

There have also been attempts to explain senescence based upon a series of predictions about how the age of organisms at reproductive maturity, fecundity, lifespan and the timing of the onset of senescence would all interact in the life history of a species. These latter predictions, which do not depend at all on details of the mechanisms of selection of

senescence effector genes, have been validated by numerous experiments over the past several decades.

In conclusion, aging is an active field of Darwinian medicine.

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Part 2

BASIC MECHANSIMS OF DARWINIAN MEDICINE APPLIED TO CHRONIC NONCOMMUNICABLE DISEASES

Chapter 5

ROLE OF ATAVISTIC TRAITS IN THE DEVELOPMENT OF CANCER

Cancer, which is an important cause of death in modern societies, is a concern of Darwinian medicine. Cancer is an abnormal growth of cells which proliferate in an uncontrolled way and spread or metastasize to other tissues in the body. It is a group of more than 100 different diseases. Cancer may affect any tissue of the body and may have many different forms in each body area. Most cancers are referred to after the type of cell or organ in which they begin. If a cancer metastasizes, the new tumor is referred to according to the name of the original or primary tumor. Atavism, heterochrony and a mismatch between the cell programming and the current environment are among the mechanisms of Darwinian medicine which have been correlated to cancer. Thus, evolution of cancerous tumors is subject to Darwinian principles.

During cancer development there is a sequence of mutation of cells followed by promotion or clone expansion. This sequence has an interesting similarity with the neo-Darwinian theory of evolution. Mutations in somatic cells result in some dividing faster than others, in some cases generating neoplasms. Neoplastic mutation in a cell is a cellular "macroevolutionary' event in which cells return to the

expression of normally quiescent ancestral, juvenile, or embryonic traits and behavior at an inappropriate stage in their ontogeny through variation or rearrangement of regulatory genes. Therefore, there is cellular heterochrony in the development of cancer. Prolactin and thyroxine have been proposed to play an important role in tumorigenesis and may mediate the atavistic or heterochronic development and possible metamorphosis of retro differentiated malignant cells.

After the mutation of the cells there is somatic selection. It depends on interactions between environmental selection forces and cell phenotype since neoplasms grow in complex cellular ecosystems. As in neo-Darwinian theory, selection is represented by the elimination of the less fit. The selection of mutated cells would mainly consist in the acquisition of resistance to apoptosis that diminishes the cell's survival, with selection of tumor cells at the expense of the host.

Genes related to cell cooperation in a multicellular organism are also responsible for cancer. Genes responsible for cellular cooperation that evolved with multicellularity about a billion years ago are the same genes that malfunction to cause cancer. This is a characteristic of primitive forms of existence. Cancer is therefore, an atavistic condition that occurs when genetic or epigenetic malfunction unlocks an ancient 'toolkit' of pre-existing adaptations, re-establishing the dominance of an earlier layer of genes that controlled loose-

knit colonies of only partially differentiated cells, similar to tumors. The existence of such a toolkit implies that the progress of the neoplasm in the host organism differs distinctively from normal Darwinian evolution. Malignant cells get adapted as if returning to a more primitive stage where there is atavistic regression to survive under unfavorable conditions.

Therefore, they cease obeying the growth-regulating mechanisms in the organism and acquire the potential of unlimited division and accelerated growth as do unicellular organisms or their forms resistant to damaging factors in the environment and in the host organism. Thus, cancer is a natural self-protective response of the cells to the biological, physical and chemical damage and oxidative stress. Therefore, malignancy can be viewed as the consequence of an evolutionary variety of the general biological resistance of cells to damage and stress in order to survive.

Furthermore, tumor cells also acquire parasitic features. With the regression of the cells to the atavistic parasitic state, the synthesis of dormant endotoxin is activated together with an enhanced expression of evolutionary resistance-related genes and oncogenes. The potential role of atavistic endotoxin in carcinogenesis has been proposed and the presence of an antigen identical to the endotoxin of gram-negative bacteria in tumor cells has been confirmed. Atavistic endotoxin, produced and secreted by

proliferating tumor cells, should cause chronic cachexia and septic states in cancer patients, similarly as in cases of endotoxemic septic shock where the endotoxin of gram-negative bacteria is the main pathogenic factor. Normal tissue extracts do not increase the endogenous level of natural immunity to endotoxin, indicating the absence of a foreign antigen such as endotoxin in normal cells which are naturally devoid also of other parasitic features such as invasiveness and metastases, whereas tumor cells, during a prolonged latent period of carcinogenesis, acquire resistance to harmful factors, lose most of their genetic, antigenic, morphological and biochemical properties and become parasitic so as to survive in unfavorable conditions. Natural specific antibodies to endotoxin can be helpful in creating new immunotherapeutic methods.

Mechanisms to reduce cancer risk have also evolved particularly in species having long lifespan. The possibilities of such mechanisms include:

a) Lowering somatic mutation rates. However, the maturation rates do not appear to differ between mice and humans.

b) Adding redundancy of tumour suppression genes. Humans have more than mic and probably whales have more than humans.

c) Eliminating proto-oncogenes. The possibility of trade-offs with these genes remains unknown,

d) Changing tissue architecture by reducing stem-cell turnover. Neverhteless, there exists no evidence for or against this possibility.

e) Evolving an immune system that more efficiently detects and kills incipient tumours. There is still no evidence for or against this hypothesis.

f) Evolving cells more sensitive to the induction of apoptosis when expressing signals of DNA damage. Again, no evidence for or against this possibility is known.

g) Starting life with shorter telomeres to limit intrinsic capacity to proliferate. The possibility of trade-offs with aging remain unknown.

Resistance to chemotherapy for the treatment of cancer has also been related to mechanisms involved in Darwinian medicine. The development of tumor cells is closely related to the mechanisms of general evolutionary resistance to damaging factors. Evolutionary resistance controls the process of carcinogenesis and the success of microbial and anti-tumor chemotherapy. Adaptation is characteristic of microbial cells whose resistance to antibiotics and other chemotherapeutic drugs is manifested through ATP-dependent trans-membrane transporters. The structure and function of some multi-drug transporters of resistance are conserved from microorganisms to mammals. When somatic

cells are exposed to carcinogens and develop into tumor cells, they also acquire resistance to the toxic effects of carcinogens through these same trans-membrane transporters. Therefore, resistance to chemotherapy drugs or irradiation acts through the same ATP-dependent transporters encountered in prokaryotic and eukaryotic cells. The mechanism of acquired resistance of cells to damaging factors, which becomes manifested during tumorigenic process formation, is of great significance in carcinogenesis. This resistance can be called malignant since it does not disappear, in a similar way as a clone of malignant cells.

Furthermore, cancer rates show great variation in different countries around the world, a variation only marginally explained by genetic differences. More interestingly, migrants change their risk of cancer by adapting to that of the population into which they move. These changes are not likely to be entirely due to mutagens in the environment, and selective pressure over mutated cells is essential to explain them. Mutated cells might adapt to environmental ‘niches’ better than normal cells, in a ‘gene–environment interaction’ that involves the history of the genetic changes the cell has undergone and the kind of environment in which it happens to live. This hypothesis complements the atavistic origin of cancer with the hypothesis of diseased due to mismatch between the cell programming and the current environment.

Therefore cancer, in the view of Darwinian medicine, might be a consequence of atavism, heterochrony and a mismatch between the cell programming and the current environment.

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Chapter 6

POSSIBLE ROLE OF ECOLOGICAL ANTAGONISTIC PLEIOTROPY OF EVOLUTIONARY TRAITS IN OBESITY, METABOLIC SYNDROME AND DIABETES

Obesity, metabolic syndrome and diabetes might be the consequence of ecological antagonistic pleiotropy since our current lifestyle (diet and sedentarism) is in disagreement with our evolutionary design adapted to famine and an active way of life. The primary causes of death during most of the history of humanity included famine and infection. Therefore, evolutionary pressures during the Miocene and Pleistocene periods selected for individuals with large portions of the genome involved in the accumulation of nutrient stores favoring individuals who were able to perform gluconeogenesis, and develop insulin resistance, promoting a thrifty genotype with accumulation of fat deposits. It also selected genes dedicated to inflammatory responses and innate immunity that are able to counteract infection and allow for survival to trauma (Figure 1). In addition to protection from periods of food scarcity, fat stores constitute the origin of the energy needed to synthesize acute phase proteins which form part of the inflammatory responses, therefore connecting nutrition and inflammation

The human evolutionary genetic design was adaptive to our previous lifestyle; however, it is poorly adapted to the

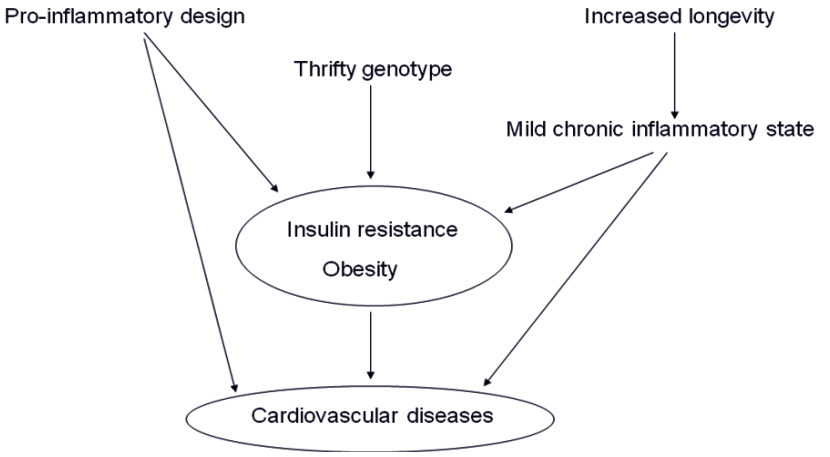

Figure 1 The selection of a pro-inflammatory design and of a thrifty genotype favored insulin resistance, obesity, diabetes and promoted the development of cardiovascular diseases.

modern environment dominated by increasingly sedentary habits, an abundance of high-carbohydrate foods, and reduced risk of mortality due to common infections. Agriculture and domestication of animals have also generated a diet rich in omega 6-fatty acid and saturated fat since animals are now fed with grains instead of their natural diet.

Obesity, metabolic syndrome and diabetes have inflammation as an underlying cause. The adipose tissue characteristic of the thrifty genotype liberates cytokines such as leptin that control the function of the immune system, acute phase reactants and inflammation. The absence of leptin is related to an increase in vulnerability to infections.

Low-grade inflammation caused by the secretion of pro-inflammatory cytokines by adipocytes together with alterations in the innate immune system due to our pro-

inflammatory genotype, are linked to insulin resistance, diabetes and cardiovascular diseases.

The adipose tissue characteristic of the thrifty genotype liberates cytokines such as leptin that controls the function of the immune system of lipoproteins, acute phase reactants and inflammation. The absence of leptin is related to an increase in vulnerability to infections.

Evolution of human nutrition.

Six million years ago, human primate ancestors lived in the woods of Eastern Africa and their diet was comprised of leaves, roots, fruits and nuts. The main macronutrients consumed were carbohydrates having low glycemic index and individuals exerted high physical activity. Human ancestors commonly faced periods of feast followed by periods of famine.

Later on, the climate became dyer and colder and the forests in which our ancestors lived disappeared and were replaced by arid grassland. This change forced human ancestors to move to the coastlines.

Human ancestors migrated out of Africa and found fertile grounds near rivers that enabled the natural growth of wild crops (cereals and legumes) and where four of the most important domesticated animals (cows, goats, sheep and pigs) could be found, allowing for the development of agriculture and farming. With domestication, animal diet

changed to feed grain (rich in fatty acids omega-6) and increased fat deposits under the skin, within the abdomen, between and within muscles. Fatter animals served as food for humans. Dairy products are high in saturated fats which increase coronary artery disease. In villages, women could make clothes to protect themselves from the cold weather, leaving aside adaptive thermogenesis. An increase in fat consumption therefore led to obesity.

The advent of the industrial revolution increased cereal production and the composition of the diet significantly changed. Highly processed cereals were rich in carbohydrates, and omega-6 fatty acids, but low in omega-3 fatty acids and antioxidants, in comparison with leafy green vegetables. Refined sugars began to be consumed in large-scale in processed food and beverages that resulted in significant postprandial hyperinsulinemia exposing the disadvantages of the insulin resistant genotype.

Hyperinsulinemia, resulting as a consequence of insulin resistance, led to obesity due to the lack of the anabolic effects of this hormone upon lipid metabolism; lipogenesis was increased in adipocytes, lipid catabolism decreases, thermogenesis was lowered, and muscle mitochondrial oxidative capacity was increased. Insulin resistance that is a state in which insulin is incapable of exerting its biological effects lowering plasma glucose levels was favored. Insulin resistance is a link between MS, glucose

intolerance, hypertension and dyslipidemia and is therefore related to cardiovascular disease.

The sodium consumption was dramatically increased, while potassium, complex carbohydrates and fiber were substantially decreased; saturated fatty acids, omega-6 and trans-fatty acids replaced the unsaturated fatty acids and omega-3. The increase in sodium consumption increased water retention by the body and therefore favored hypertension. The consumption of micronutrients decreased while the calorie intake increased.

During the industrial revolution, the screw press and solvent extraction processes made possible the extraction of oil from seeds and its hydrogenation. The hydrogenation process increased the formation of trans-fatty acids in meals that cause increases in serum cholesterol which is related to atherosclerosis. Modern aquaculture produces fish that contain less omega-3. The composition of chicken egg has high concentrations of omega-6 to omega-3 ratio 19:9, while milk and cheese of animals fed with grains lacks eicosapentaenoic (EPA), docosahexaenoic (DHA) and arachidonic (AA) acids.

Selection of a thrifty genotype

The thrifty or diabetic genotype theory was proposed by Neel (1962), based on epidemiological studies in North-West America, where there is a high incidence of type-2

diabetes. The theory proposes that "economic or diabetic genes" were selected during evolution when food was scarce and have been inherited to this day. These genes allowed individuals to store excess food as fat when it was available, and then benefit from these stores during long periods of famine. Evolutionary medicine suggests that diseases are the result of an incompatibility between human evolutionary design and the current style of human life. Genes were selected to adapt human beings to their ancestral nutrition style and rate of activity over millions of years. Today, environmental conditions have changed, and humans face new conditions with an evolutionary design adapted to previous conditions that leads to obesity and diabetes. The study of the nutrition of human ancestors throughout evolution described in the previous section may help us understand the role played by insulin and insulin resistance in survival and the importance of the selection of a thrifty genotype; however, these genes may predispose to diseases in an environment with abundant sources of food rich in carbohydrates.

As an example of more recent gene selection to ancestral conditions, the presence of a functional variant of the A1 gene ATP binding cassette transporter (ABCA1) is unique to populations of Native Americans and their descendants. This gene is determinant for low levels of HDL-C and may have contributed to the evolution of adaptation of Native American populations. However, nowadays the

presence of this transporter leads to a higher incidence of diabetes, multiple sclerosis and obesity. This variant of the gene may also confer protection against certain infectious and / or thrombotic disorders.

One of the advantages of obesity resulting from the acquisition of a thrifty genotype was cerebral growth and female reproductive fitness. The reproductive and child rearing processes depend heavily on the accumulation of adipose tissue. Sexual selection acted upon adipose tissue distribution and contributed to reproductive fitness by altering the opportunities to mate and leading to the selection of individuals bearing this trait. It also contributes to the mechanisms that regulate female reproductive function. Leptin acts on the availability of metabolic fuels in female reproduction to supply energy to the offspring. Adipose tissue also supplies the energy needed for the development of the human brain early in life, when this organ contributes importantly to body weight. It acts as a reserve in the newborn and infant to face growth.

An alternative theory to the thrifty genotype hypothesis has been proposed. It states that genetic drift rather than positive selection could have been a dominant factor for the evolution of obesity. According to this theory, starvation periods would have caused great mortality and it concludes that if only the individuals carrying the thrifty genotype were selected, nowadays everyone would be obese. It explains that

the thrifty genotype genes would have disappeared since obesity might have been selected against by the risk of predation and by the sporadic occurrence of famine in current times. It proposes that later on, the risk of predation was diminished because of the development of social behavior, the invention of weapons, and the discovery of fire and the distribution of body fat gradually changed favoring obesity due to mutations and drift. This could be the explanation of why nowadays most people are not obese.

Obesity is also associated to changes in the intestinal microbiota during evolution. The internal microbiome has adapted to diet changes and coevolution has played an important role in the relation between the host and the pathogen. Our bodies provide habitat and nutrition for organisms which improve our physical condition by metabolizing food which our digestive enzymes cannot break and that constitute the human microbiota. These organisms contribute with 10% of the energy required by the human bodies. Our microbiota also protects against harmful microorganisms and participates in the development of the immune and gastrointestinal systems. In obese people, the intestinal microbiota favors the accumulation of fat since it includes bacteria that are able to metabolize ingested carbohydrate and provide additional energy that contributes to fat accumulation.

Early developmental programming of obesity, metabolic syndrome and diabetes

The theory of the thrifty genotype has been extended to scarce food during early stages of development and stressful conditions leading, through epigenetic changes, to low weight at birth that results in a higher incidence of metabolic and cardiovascular diseases during adult life.

Changes in nutrition during critical windows of development may increase the risk of presenting metabolic diseases upon reaching adulthood. Critical windows around birth occur in many tissues and organs and coincide with rapid cell division stages. During these windows a programming of reference values of functions may occur. Programming is the process by which a stimulus or insult in a critical period of development has lasting effects, which change the course of the individual's life making him more susceptible to developing certain diseases.

The concept of "critical window" postulates four characteristics:

1. It is considered to cover the pre- and peri-natal stage. However, puberty, due to the great changes associated with hormonal maturation, could also be considered as “critical windows”.

2. It occurs in a relatively short time during the developmental sequence. It may consist of hours, days,

weeks or months, depending on the species as well as the longevity of organisms belonging to that species.

3. When an endogenous or exogenous stimulus occurs in this period, it has long-term effects on the subsequent development of life.

4. This same stimulus has a very small effect or does not have it when the "critical window" ends.

The concept of "critical window" includes a lapse of time when there is rapid growth and / or maturation and will be characterized by a high rate of growth, cell division and apoptosis. It includes a period when establishment values of regulation of functions takes place.

The first response of a fetus to poor nutrition is tissue catabolism. Longer malnutrition leads to a slower growth of the organism, favoring in the fetus the ability to survive with a reduced consumption of substrates and with a low metabolic rate. The reduction of the rhythm of growth leads to alterations in the proportional growth of the organs, being the organs that are in fastest growth at that time the most affected. One way for the fetus to protect vital organs is to alter the distribution of blood flow, increasing it to the most important organs and decreasing it in other regions. Poor nutrition also alters the secretion of hormones that participate in interactions between the mother, the placenta and the fetus. In particular, the level of insulin-like growth factor IGF which is a growth determinant is altered.

Neonates with slow growth have less subcutaneous fat stores but similar intra-abdominal fat to normal-weight neonates. Low weight favors energy allocation to specific tissues or fuel depots. The organism can therefore adjust the distribution of nutrients for the maintenance of specific tissues adapting to adverse conditions. The life history theory explains the trade-offs in the distribution of nutrients to tissues and natural selection determines the best strategy. Age, gender, body size, growth rate, current energy stores and reproductive status constitute determining factors influencing the strategy for the best distribution of energy.

All these variations caused by a change in the metabolism of the individual in early stages of life become programming factors in individuals, rendering them more susceptible to diseases when they reach adulthood. There is a higher risk to develop obesity, metabolic syndrome and diabetes. At present there are numerous demographic studies that demonstrate the association of low birth weight with these pathologies.

The effects of high carbohydrate diets before and during pregnancy and during lactation have also been studied, with a higher prevalence of metabolic syndrome and hypertension in the offspring when they reach adulthood.

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Chapter 7

ECOLOGIC ANTAGONISTIC PLEIOTROPY AND HETEROCHRONY IN CARDIOVASCULAR DISEASES

Evolution Cardiovascular diseases

Insulin resistance and inflammatory responses which were favored during evolution constitute risk factors for the development of cardiovascular diseases. Risk factors for atherosclerosis and diabetes overlap and there is a propensity of diabetic patients to have premature atherosclerosis leading to the hypothesis that both share an inflammatory and perhaps genetic basis.

A poor adaptation to high ingestion of salt is also a cause of cardiovascular diseases. Humans and related species evolved in a salt-free environment over millions of years with intense evolutionary pressure for the selection of salt conserving genes. The recorded history confirms how rare and inaccessible salt has been until recently. The human species was therefore adapted to very low salt intake and nowadays it is consuming high amounts of salt. This change in the diet represents an evolutionary mismatch with catastrophic health consequences. More than a quarter of human populations suffer from hypertension. World Health Organization (WHO) and many governments have now taken action to reduce dietary intake of salt in an effort to reduce the

incidence of hypertension and the associated cardiovascular morbidity and mortality.

The orthograde human posture and locomotion in the form of anatomical pendulums and harmonic cycles is unique among mammals and a poor adaptation to this condition has also been proposed as a cause of hypertension. The study of the evolution of posture of humans has been of great interest to anthropologists, archaeologists, anatomists, physiologists, evolutionary biologists, doctors and specialists. About 30 hypotheses have been expressed over the last 100 years. Ideas have emerged that bipedalism gradually evolved for 7 million years of selective forces. Bipedalism probably evolved in particular environments such as the savanna, or arboreal life in forests, or both. Since the end of the last century, archaeological evidence has suggested that bipedalism appeared in a wet environment. The amphibian theory has been proposed, which suggests that bipedalism began in forests not far from the coasts, lakes, ponds or canals, where primitive ancestors found food (fish, molluscs and crustaceans) in rich brackish waters. This activity forced them to maintain a standing position.

Research on bipedalism in humans has focused on studies of bone remnants and anthropological elements of hominids or higher primates and therefore relatively little is known about physiological adaptations. Many researchers have considered that the orthostatic syndromes are due to a

dysfunction of the mechanisms that maintain normal hemodynamics during the process of standing up.

It should be mentioned that emotional stimuli can also trigger a reflex similar to the orthostatic reflex. Reactions such as fear-bradycardia syndrome in the opossum in the presence of a predator have been studied. The animal turns to a deathlike syncope state and expells a bad odor to make the aggressor run away. Primates observing a snake also have a response similar to the orthostatic reflex. Evolution has partially solved the gravitational effect creating hemodynamic conditions during standing up through mechanisms mediated by neural activity and venous and muscular compensation that can be potentially harmful. Adaptation is not perfect and can lead to the development of hypertension.

Development, low birth weight and hypertension

The evolution of the species and the development of the individual are determinants for the risk to health in the adult since they program and establish the capacities according to the demands that the species has faced throughout history and according to individual development. Low birth weight is a well-known risk factor that increases childhood morbidity and mortality. Additionally, it has been observed that it can increase the risk of suffering certain pathologies in adulthood such as coronary heart disease, hypertension and diabetes. Low birth weight forces the

individual to develop strategies to survive in the early stage having a cost on the risk in health in the adult.

Neuroendocrine mechanisms are being studied in the programming of increased risk to cardiovascular diseases, in particular the participation of the hypothalamic-pituitary-adrenal axis as an agent that determines the placement of resources depending on the conditions of pregnancy, postnatal environments thus impacting on the health-disease balance in the adult.

Numerous animal models have been studied to determine the association of low birth weight with the development of hypertension in adult life. One of them is a model of protein malnutrition. Limiting protein intake in the mother during pregnancy generates low weight products that tend to develop hypertension when they reach adulthood. In another model, the uterine arteries are ligated to decrease perfusion to the placenta. The products of these pregnancies are small and develop hypertension when they reach adulthood. In another model, dexamethasone is injected to pregnant mothers in stages near childbirth. Again, the products are small in size and develop hypertension later in their lives. All these models support the idea that low birth weight programs individuals to develop hypertension in adult life.

The effect of a diet high in salt, before and during pregnancy and during breastfeeding and the first days after

weaning has been studied, finding that the predisposition to suffer from hypertension in the adult is increased. In another study, a high salt diet was administered only during pregnancy to try to find a more limited critical window and a greater predisposition to hypertension was found in adult organisms but only in females.

Changes in diet and low weight during the perinatal period alter the renin angiotensin system. As a consequence, in the treatment of this system, the structure of the vessels is modified showing less elasticity. Cardiac myocytes, which differ terminally before birth are also affected being less numerous and larger.

There is a critical window of the pancreas, in which changes in diet predispose to an increased risk of suffering from diseases in adulthood such as obesity and metabolic syndrome. During it changes occur in plasma glucose and insulin concentrations that could be accompanied by changes in vascular contractility. Also, variations in feeding during this critical stage that occurs postnatally could predispose to an increased risk of developing hypertension in the adult.

During the critical window of the pancreas the contractility of the aortas is increased by raising plasma glucose and insulin levels but without reaching the levels of rats with metabolic syndrome. Relaxation is diminished at a level similar to that of the aortas of rats with metabolic syndrome. A diet high in sucrose during the critical window

raises blood pressure in the same proportion as the administration of sucrose continues from weaning to adulthood. The contractility of the aortas does not increase significantly with the administration of sucrose during the critical window, but the relaxation decreases significantly.

Epidemiological studies

The first correlations between a nutritional deficit in childhood and a vulnerability to coronary heart disease in adulthood are reported around the 70's in the United Kingdom. Later, Wadsworth et al, in 1985, reported that blood pressure in adulthood was inversely related to birth weight in men and women born in 1946. In 1987, in Hertfordshire, the first retrospective study was performed with individuals born between 1911 and 1930, who showed low birth weight or low weight during the first year of life. This work was published by Barker et al 1989, trying to find an explanation for the high incidence of both hypertensive people and deaths from cardiovascular diseases in adulthood that occurred in that region.

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Chapter 8

RESPIRATORY AND DIGESTIVE DISEASES

Respiratory diseases have been linked to ecological antagonistic pleiotropy. Obstructive pulmonary disease could be the result of the evolution of humans having hyperactive proinflammatory genes. Asthma could be the result of the poor adaptation to a highly hygienic way of life. Idiopathic pulmonary fibrosis could be the result of the expression of a fetal phenotype due to the activation of atavic genes. Regarding digestive diseases, Crohn's disease has also been postulated to be a consequence to a poor adaptation to highly hygienic conditions.

Although applying Darwinian medicine to clinical practice may not have an immediate impact on day to day therapeutic decisions for respiratory and digestive tract diseases, it may impact the treatment of symptoms such as coughing, mucus secretion and diarrhea.

Respiratory diseases

The genetic predisposal to develop chronic obstructive pulmonary disease (COPD) may come from the adoption of hyperactive proinflammatory genes (genes encoding an excessive inflammatory response, acquired by spontaneous mutation evolution of) by pressure of natural selection due to

a high prevalence of infectious diseases in ancient humans. Hyperactive proinflammatory genes are considered to have evolved as a reproductory advantage, because these genes were beneficial for protecting against lethal infections in the Stone Age. According to this hypothesis, our ancestors are considered to have acquired hyperactive proinflammatory genes at some point in the past by spontaneous genetic mutation. These hyperactive proinflammatory genes are seen as mutational genes that can induce hyperinflammatory responses to external stimuli. High responders with a gain-of-function allele might have left more offspring than low responders without this allele if this allele conferred higher resistance to lethal infections such as tuberculosis, malaria, and smallpox. The high responder genotype might thus have gradually spread within the population under the pressure of natural selection. In the Stone Age, however, average lifespan was only about 30 years. Humans therefore had little opportunity to survive until old age, when chronic diseases due to hyperactive proinflammatory genes manifest.

Hyperactive proinflammatory genes, which would have protected human beings from dangerous infections in the Stone Age, may be responsible for modern chronic inflammatory diseases, such as COPD. Inflammatory responses are beneficial, even in the elderly, up to the point where they provide protection against infections; however, chronic activation of such genes, such as by exposure to

cigarette smoke, is harmful to the body. However, these adverse effects may not subject the genes to the pressure of natural selection, because the adverse effects are manifested long after reproductive age. The success of reproduction and prosperity of the descendants may hold higher priorities for these genes than health maintenance in old age. In regard to hyperactive proinflammatory genes, it is probably beyond all expectation that humans have probably come to live to such an advanced age when the adverse effects of air pollution on health become manifest.

An example of atavic characteristics present in cells from a diseased state is found in idiopathic pulmonary fibrosis. In this disease, cells show fetal phenotypes.

Asthma has been proposed to be the result of the hygiene hypothesis. This hypothesis argues that since humans have begun to be reared in more hygienic circumstances and exposure of humans to microorganisms such as helminthic worms has been decreased the incidence of certain diseases has risen.

Coughing, mucus secretion may be seen as evolved mechanisms for expelling the infectious microbe, and while it seems counter intuitive to leave these symptoms untreated, there is some suggestion that blocking these normal defences may extend the illness duration. However, if the severity of the symptoms exceeds that which is adaptive, then medical intervention would become necessary.

Digestive tract diseases

The hygiene hypothesis may also been applied to Crohn's disease which is an inflammatory disease of the bowel that can be very debilitating. Recent evidence suggests its incidence has risen as gastrointestinal worm infection has fallen. Thus, the disease might be caused by the defense mechanisms against gut parasites now targeting the gut wall. Indeed, there are promising clinical trials in which patients suffering from Crohn's disease are treated with either pig hookworms or their extracts.

An evolutionary perspective can lead to new clinical insights into providing an evaluation for presence of diarrhea which may be seen as evolved mechanisms for expelling the infectious microbe. Blocking this normal defense may extend the illness duration and medical intervention might only become necessary when the severity of the symptoms exceeds that which is adaptive.

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Chapter 9

NEOTENY AND EARLY PROGRAMMING OF PSYCHIATRIC AND NEUROLOGICAL DISEASE

Evolution and the brain

The development of the brain has been linked to changes in nutrition during evolution. When hunted large predators became a part of the human diet, low carbohydrates and lots of protein were ingested and the diet was enriched in micronutrients such as iron, retinol, zinc, vitamin B_{12}. Unsaturated fatty acids were also increased in the diet when fish was included (with a balance of fatty acids omega-3 and omega-6, ratio 1:1). These new components of the diet provided enough fuel and building blocks to facilitate encephalization and the development of intellectual capacity.

Fifty percent of total body glucose is consumed by the brain even if it constitutes only 2% of the body mass and the brain depends exclusively on glucose as its energy source consuming more than 20% of total resting expenditure. Therefore, the theory of the “selfish brain” that postulates that insulin resistance might have been favorably selected during evolution to avoid the danger of hypoglycaemia to the brain.

The brain is able to maintain a constant flux of large amounts of glucose in the presence of powerful competitors such as fat and muscle tissue by activating a stress system that includes the HPA axis and the sympathetic nervous

system. Activation of the sympathetic-adrenal system inhibits glucose uptake by peripheral tissues by inhibiting insulin release and inducing insulin resistance and by increasing hepatic glucose production. Furthermore, insulin signals the brain so that it is the first organ to replenish its source of glucose before other organs consume it. Gastrointestinal hormones such as leptin may represent an evolutionary adaptation. Leptin crosses the blood brain barrier informing the brain about the feeding and nutritional status of the rest of the body and hypertriglyceridemia which occurs during starvation inhibits leptin transport. Inhibition of leptin could have had survival advantages during starvation. Therefore, to compensate for the metabolic cost of encephalization, lower mass-specific metabolic rates in other tissues like the gut were favored.

Aerobic glycolysis that includes non-oxidative metabolism of glucose despite the presence of abundant oxygen, accounts for 10–12% of glucose used by the adult human brain. The rate of aerobic glycolysis varies regionally in the resting state. Brain aerobic glycolysis may support synaptic growth and remodeling. Aerobic glycolysis increases during childhood, when synaptic growth rates are highest.

In resting adult humans, aerobic glycolysis correlates with persistence of gene expression typical of infancy and therefore with a neotenic pattern. In brain regions with the highest aerobic glycolysis there is increased gene expression

which is related to synapse formation and growth. In contrast, regions with high oxidative glucose metabolism express genes related to mitochondria and synaptic transmission. Brain glucose uptake exceeding oxygen use is decreased with age resulting in loss of brain aerobic glycolysis. Whereas the brain regions where brain glucose uptake, oxygen utilization and blood flow take place remain largely stable with age, brain regions where aerobic glycolysis happens change significantly. Brain regions with high aerobic glycolysis in young adults show the greatest change, as do regions with prolonged developmental transcriptional features (neoteny). The normal aging human brain thus undergoes characteristic metabolic changes, largely driven by global loss and regional changes in brain aerobic glycolysis.

Many feeding substances have evolved that affect neurogenesis, neuroprotection, and cognition. Humans might have undergone changes in the pattern of neurotrophin expression resulting from a positive selection for heightened intelligence which is in correlation to dietary deficiency. During neonatal neurogenesis mammals produce an excess number of neurons whose eventual destruction is dictated by neurotrophic factors. An altered pattern of neurotrophin expression such as brain derived neural factors (BDNF) during neurogenesis could determine a larger adult brain.

Heterochrony seems to play an important role in human evolution particularly for brain development.

Heterochrony is defined as evolutionary change in the rate or timing of developmental processes. Early researchers suggested a single heterochronic shift towards neoteny, defined as the persistence of embryonic, fetal, or juvenile features of the ancestral species into adulthood of the descendants by slowing of growth and delayed maturation. Childhood provides a basis for neoteny of the human brain. Childhood is the period following infancy, when the youngster is weaned from nursing but still depends on older people for feeding and protection, evolved as a new stage hominid life history, first appearing, perhaps, during the time of *Homo habilis.* The value of childhood is often ascribed to learning many aspects of human culture and provides ‘‘extra’’ time for brain development and learning.

Prolonged youthfulness in humans, as a consequence of neoteny may be considered as advantageous in modern life and a process that could be termed 'psychological neoteny' has been proposed as a correlation of Darwinian medicine with neurosciences. The mid-20th century was characterized by the rise of the boy-genius, since prolonged youthfulness began to be considered as advantageous for modern life. A child-like flexibility of attitudes, behaviors and knowledge is probably adaptive in modern society because people need to change jobs repeatedly, learn new skills, move to new places and make new friends. This adaptation is achieved by postponing cognitive maturation. People having cognitive

flexibility tend to thrive and succeed, and have set the tone of contemporary life. Since psychological neoteny is considered as having advantages for the new way of life, many contemporary individuals, never actually become adults. However, the faults of youth such as short attention span, sensation- and novelty-seeking and a sense of cultural shallowness are retained with these virtues.

Althoug neoteny-related non-specialisation has been assumed to be of adaptive value to cope with different ecological environments, neoteny may also play a role in the origin of psychiatric disorders. Some diseases may be due to a failure of neoteny. Neotenic abnormalities may underlie negative symptoms of dementia praecox, a chronic mental illness that strikes individuals as they become adults. It is postulated that a possible mechanism in the etiology of dementia praecox is the failure of regulator genes to program structural genes to produce enzymes necessary for neoteny. Positive symptoms of the disorder may be conceptualized as the organism's aberrant response to this activation failure. The role of regulator genes in chronic illness may prove a significant avenue for further investigation. The progressive delay in maturation (neoteny) to increase brain size and intelligence has also been proposed as a cause of psychoses which are disorders arising from variation in the genes controlling hemispheric asymmetry.

Neoteny has also been implied in neurological disorders in adults. Brain diseases such as multiple sclerosis have been proposed to be the result of the hygiene hypothesis. Patients with multiple sclerosis with worm infections developed symptoms significantly more slowly than those without the helmintic parasites. Clinical trials are presently underway to determine whether treatment with worms has therapeutic value.

Early stages of development and the nervous system

Probably, one of the best- known examples of a critical window, which may lead to ecological antagonistic pleiotropy when organisms reach adulthood, is the need of thyroid hormones for the normal development of the nervous system at birth. When thyroid hormones are absent, the result is the development of cretinism. It is known that a newborn lacking a thyroid gland can have a completely normal appearance and function because he has received thyroid hormone from the mother during intrauterine development. However, a few weeks after birth, movements become lazy, and their mental and physical development is considerably delayed. The treatment of these patients at an early stage means the resumption of normal physical growth; but if it is not carried out in the first months of life, intellectual development will cause a permanent delay in the development of the nervous

system. This is probably due to the fact that the physical development of the neurons of the central nervous system is very rapid during the first year of life and any delay in this time produces considerable disorders. Therefore, the first months of life are considered a critical period of the development of the nervous system, in which there is a dependence on the presence of thyroid hormones and other environmental conditions.

During development of the human brain, regulation of nerve cell proliferation, and selective stabilization of synapses play crucial roles. Nerve cell proliferation is supposed to be regulated by the genome, while selective stabilization is proposed as developing in a more plastic manner. Genetic alterations of the regulation of neuroblast proliferation lead to epigenetic rearrangements in selective synapse stabilization, thus producing significant changes in cerebral connectivity. Dendritic spine density in childhood exceeds adult values by two to threefold and begins to decrease during puberty. However, overproduction and developmental remodeling, including substantial elimination of synaptic spines, continues beyond adolescence and throughout the third decade of life before stabilizing at the adult level. Such an extraordinarily long phase of developmental reorganization of cortical neuronal circuitry has implications for understanding the effect of environmental impact on the development of human

cognitive and emotional capacities as well as the late onset of human-specific neuropsychiatric disorders.

The prolonged developmental plasticity in the associative frontal cortex in human allows for an unprecedented opportunity for acquisition of the highest level of cognitive abilities but also is susceptible to the formation of abnormal circuitry that is manifested in late-expressed neuropsychiatric disorders. Schizophrenia might be caused by a fault in programmed synaptic elimination during adolescence since there is a reduction in cortical synaptic density and a re-organization of brain function that must accompany it that had been reported to take place around adolescence. This disease might be caused by the elimination of too many, too few or the wrong synapses. The existence of a process of elimination of synapses and particularly its timing, make it an attractive candidate as a probable cause of psychosis. Psychotic illnesses are rare before puberty, but they have an extended distribution of onsets thereafter.

The exposure to environmental conditions, such as stress, during critical periods in early life may cause epigenetic programming modifying the development of pathways that lead to stable and long-lasting alterations in the functioning of mediators during adulthood, determining the risk of or resilience to stress related disorders. Although epigenetic cues may remain fixed and/or even be inherited in

the next generation, they may be also dynamically altered throughout the lifespan, in contrast to genetic information.

Mechanisms controlling mitochondrial function, protein folding in the endoplasmic reticulum and nuclear processes such as telomere length and DNA repair may be subject to epigenetic cues that relate the genomic expression and environmental exposures in early stages of life. They may also be involved in the appearance of neuropsychiatric diseases during adulthood. Mitochondrial function and protein folding in the endoplasmic reticulum are associated with oxidative stress and elevated intracellular calcium levels and may also underlie the vulnerability for neuropsychiatric disorders. Mitochondria provide key metabolites such as β-nicotinamide adenine dinucleotide (NAD+), ATP, α - ketoglutarate and acetyl coenzyme A (acetyl CoA) that are required for many transcriptional and epigenetic processes. They are also a source of free radicals. On the other hand, epigenetic markers in nuclear DNA determine mitochondrial biogenesis. The endoplasmic reticulum (ER) is the subcellular organelle in which secretory proteins are folded. Many environmental factors stop the ability of cells to properly fold proteins and modify post-translationally secretory and transmembrane proteins leading to endoplasmic reticulum stress and oxidative stress. ER functioning may be epigenetically determined. Chronic ER stress is emerging as a key contributor to a growing list of

human diseases, including neuropsychiatric disorders. Telomere loss causes chromosomal fusion, activation of the control of DNA damage-responses, unstable genome and altered stem cell function, which may underlie neuropsychiatric diseases. The length of telomeres is related to oxidative stress and may be epigenetically programmed. Pathways involved in DNA repair may be epigenetically programmed and may contribute to diseases.

Observations have also been made with malnutrition at birth and a higher glucocorticoid level has been found in malnourished products as well as in their mothers. It is thought that hormonal changes induced by responses to violence in the future mother during pregnancy, increase glucocorticoid levels and facilitate an abnormal metabolic response in the product. In addition, other studies indicate a persistence of insulin resistance in newborns since the early stages, from mothers that underwent violence. Corticotrophin releasing factor, vasopressin, oxytocin, natriuretic hormones, angiotensin, neuregulins, some purinergic substances, and some cytokines contribute to the long-term abnormal stress responses and to modulation and restructuring of cardiovascular regulation networks. The synthesis, release, and receptor expression of these mediators seem to be under epigenetic control since early stages of life, possibly underlying stress related disorders.

Social and cultural environmental factors influence the development of susceptibility to diseases in adulthood since the peri-natal stages of life. Sociotype describes the way in which interactions between social, cultural and environmental factors influence health. It plays a role as important as that of the genotype and phenotype in the balance of the health/disease processes during all the life span. Attachment forms part of the sociotype and is defined as the innate biological system that characterizes the link between an infant and a bonding figure. It increases the possibility of survival to a reproductive age and determines empathy and intimacy that when incorrectly established may be the cause of a number of pathological conditions in the adult life. Different types of attachment have, as a consequence, physiological and endocrinological alterations that result from the exposure to stressful and/or traumatic events during early stages of life. These constitute long-term plastic changes in structures in the central nervous system that produce in alterations in signaling molecule production that may arise from epigenetic cues established during early stages of life in trauma- exposed subjects and that may lead to increased risk of diseases in adulthood. Therefore, sociotype and attachment might determine epigenetic alterations that may act on biological pathways involved in neuropsychiatric diseases.

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CONCLUSION

The understanding and possible cure of many diseases might be found by following the ideas of Darwinian Medicine under a clear perspective based on population genetics, genomic advances and evolutionary ecology. A better understanding of the mechanisms behind Darwinian medicine may contribute to a better knowledge of the diseases. In the hypothesis explaining the aging process which is a predisposing factor of most modern time diseases, mechanisms such as atavistic genes, mismatch between our evolutionary design and current lifespan and antagonistic pleiotropy play central roles.

A better understanding of the biological mechanisms that underlie Darwinian medicine is linked to the concept of evo-devo with its influence on medicine which might provide us with enormous possibilities to modify the causes of diseases but whose application should be handled with care since it might allow the manipulation of the main processes which led to evolution and therefore to the appearance of life and the evolution of the human species.

The new revolution in developmental biology and its influence on medicine might provide us with a remarkable power. Investigations into regeneration, stem cells, and tissue engineering provide access to areas of “applied developmental biology” and “developmental medicine”. Due to

the importance of this field public policy will affect research directions, and perhaps we will see “off-shore” developmental biology laboratories pursuing research not sanctioned in some scientifically advanced countries and wisdom in establishing its own regulations will be required.

Evolutionary biology is central to understanding the causes of our health problems. A better knowledge and possible cure of many diseases can be found by studying the mechanisms behind Darwinian medicine. Darwinian medicine is linked to the concept of evo-devo which might provide us with enormous power and possibilities to modify the causes of diseases. In this book we discuss the participation of pleiotropism and/or antagonic pleiotropism as well atavistic genes and/or heterochrony as the main mechanisms behind the evolving field of Darwinian medicine. We analyze the influence of the environment on development and aging, and on propensity to diseases. Regarding aging, the main hypothesis, include the three mechanisms described above; atavistic genes, mismatch between our evolutionary design and current lifspan and antagonistic pleiotropy. In turn, aging is a predisposing factor of most modern time diseases. We also discuss the problems faced by the employment of stem cells in regeneration, which might be a consequence of the different developmental stages of the cells implanted and the tissue host that receives them.

Tools are being developed that may be able to alter the course of human development, human evolution, and even the evolution of the biosphere. The application of the new strategies of evo-devo and the knowledge of the mechanisms of Darwinian medicine should be handled with enormous care since they might be the origin of most of the diseases that are becoming actual global epidemics.

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