Evolutionary medicine and cardiovascular problems

Evolutionary thinking is central in biology. As Alfred Dobzhansky has expressed "In biology nothing makes sense except in the light of evolution". (1) The decodification of the human genome and other living species has confirmed the similarity of our DNA with higher primates and other mammals. Genetic studies make possible tracing the biologic history of our species to millions of years ago. However, in medical training is yet exceptional the teaching of evolutionary biology and its implementation for a better diseases comprehension. (2)

In the last two decades, efforts which had explored some difficulties of human biology and chronic diseases through an evolutionary view had emerged as a new source of thinking about medical problems. (3) Some of these explorations had focused on the most frequent cardiovascular problems as hypertension, atherosclerosis and coronary artery disease. There is no area in medicine, from pregnancy-childbirth to tumors, where pathogen mechanisms considered "biological failures" with this different approach had been tried out.

AN INTRODUCTION TO EVOLUTIONARY APPROACH DISEASES

Darwinian evolutionary thinking explains the biological variation through the appearance of small mutations that remain with more preeminence in descendants. Unlike Lamarckian thinking, which considers variations as induced by the environment and adaptable (which were expressed as "inheritance of acquired characteristics"); in Darwinian thinking changes or mutations are random. In classical conception, the selection is done on the mutated individual, if he has had the opportunity to reproduce. The four billion years of life evolution in our planet allowed diverse and fine combinations which allowed the adaptation to the variable environment conditions.

When faced with a biological finding, the evolutionary asks about the reason of that presence. In other words, which is the evolutionary advantage provided by this phenomenon. Topics considered failures or persistence of historic mechanisms now useless can be thought in a different way through the evolutionary view. Let's take two initial examples: a) blood uric acid and b) IgE and asthma.

Levels of uricemia from an evolutionary view

Levels of uric acid are higher in humans than in mammals, due to the lack of liver uricase. These levels are associated with a greater possibility of development of elevation of blood pressure (4, 5) and gout, and could be considered as an evolutionary failure or a useless hindrance. Several authors have stated a phylogenetic advantage that justifies the selection to the loss of that liver enzyme in human specie in favor of greater levels of uricemia: a) collaboration in maintaining blood pressure favoring vasoconstriction in populations with limited environmental sodium. (6) b) antioxidant properties (7) and c) a favorable role in immune response. (8) In the current nutritional environment with high salt consumption and other dietary modifications, the hyperuricemia pleiotropic effect is harmful, being associated with higher levels of blood pressure and risk of gout.

IgE's function and why asthma is so frequent

As a response to parasitic aggression, humans have suffered genetic adaptations that minimize illness manifestations, but they contribute to allergic disease. In those patients affected by different parasitic diseases high levels of IgE are observed and however the incidence of cutaneous atopy or asthma is low. (9) This has been studied in South American native populations. These settlers, living in urban areas with no exposure to parasites, have greater incidence of atopy and asthma. Evolutionary interpretation is that IgE system and bronchial hyperreactivity have been adequate systems to control parasitic, endemic infections until a few centuries and even today in populations with no shoes and drinking water. Those persons with more capacity to activate this system had an evolutionary advantage that favored survival and positive selection. If with hygienic measures parasitosis is avoided, especially helminth, that consume the activity of IgE system, against the exposure to many environmental allergens IgE system becomes a source of hyperreactivity. This is the so called hygienic hypothesis of asthma and atopy, which would explain the high incidence in populations that until recently were exposed to universal parasitosis, as the observed in African-American groups. (10) Current research has advanced to the identification of the involved genes, with the surprising finding of biological similarities of plasmodia proteins and schistosoma with humans. Resistance to malaria or schistosomiasis would be associated with bronchial hyperreactivity and atopy. (11)

Another endemic disease, falciform anemia, has a greater resistance to paludism and is an evolutionary advantage that has made easier its perpetuation. (12)

BIOLOGICAL HISTORY OF OUR PLANET ENDOSYMBIONT, OXYGEN AND INFLAMMATORY RESPONSE SYNDROME

Lynn Margulis, a brilliant American biologist, published in 1967 with the name of Lynn Sagan her

first article that led to the so called endosymbiont theory. The author stated that mitochondrias were independent bacteria that had been incorporated to other prokaryotes and reached a joint survival. (13) Her original work was rejected by 15 scientific journals obtaining then universal recognition. She has published several books focusing on the first two billion years of history of life in the earth from the symbiosis view, with different consequences to the traditional evolutionary conception, among them "Microcosmos" (14) and "Captando Genomas". (15) Her theory in several aspects contradicts the Darwinian concept of evolution by random mutation, at least in the stage of prokaryotes. The evolutionary biologist Ernst Mayr with more than 100 years of age wrote a memorable prologue to "Captando Genomas", accepting the endosymbiont hypothesis in the cell stages of initial prokaryotes, but rejecting every possible Lamarckian scope or wish of that level of symbiosis as alternative to mutation-selection in more complex animals. (16)

In the endosymbiont hypothesis, the current nucleated cell is the result of symbiotic coexistence of several bacteria that had been captured by others achieving thus a new balance. The nucleus would be made up of an archeobacteria, and mitochondrias would be made of the bacteria that have mutated with the ability to metabolize the oxygen and therefore maintain their original DNA, the origin of chloroplasts is similar, and flagella or cilia were originated in spirochetes. Scientific community has accepted this proposal, with the exception of the one regarding spirochetes, which is still in debate.

In order to support this hypothesis, it has been demonstrated that unicellular, in extreme conditions, are fragmented into smaller ones that can sustain life independently of symbiotic coexistence. An unexpected example of "symbiotic consortium" is the current organism Thiodendrom latens which is found as a fossil 2000 thousand years ago and maintains its structure with multiple threads. As sulfureous and anaerobic solutions, their long threads become spirochete that acquire independent life and are able to move and reproduce. This stable symbiotic consortium of billions of years gives support to the endosymbiont theory. (17)

So, during the first stages of evolution, evolutionary advantages of the adaptable chemical exploitation to the environment suffer an exchange that allows "acquiring genomes" absorbing some prokaryotes to other specialized, with favorable effects on survival.

The current ways of symbiosis are emphasized by Margulis, as the case of the herbivorous mammals that do not have enzymes to degrade cellulose, which is achieved with large intestines settled by bacteria which carry out that digestive function essential for survival.

Symbiotic ecosystem

Symbiotic conception has another surprising implication. The atmosphere is the result of the progressive accumulation of oxygen produced by the living species.

On the account of this researcher, the first forms of life that acquired the ability of reproduction had biological conditions very different to the current ones. The atmosphere of the planet was very similar to the current one in Mars, with 80 to 90% of carbonic anhydride and only 0.03% of oxygen. Life was anaerobic, and during these two billion years a great random biochemical experimentation of the exploitation of the available resources in the environment was produced. With the expansion of cyanobacteria over the entire surface of the planet two billion years ago which acquired the hydrogen from the water, one of the "toxic" elements that started to accumulate as catabolic product is the oxygen. Oxygen was very dangerous: not only had it made easier combustion but the release of destructive free radicals for the bacterial structure. The adaptable response was the development of bacteria that allow metabolizing oxygen with energetic advantages that as we have commented acquired their role of mitochondria when associated with other bacteria.

It is estimated that after the first two billion years oxygen concentration had been increased until the current proportion of 21% which is stable in the last hundred million years, result of a complex equilibrium in the functioning of all the life of the planet, the so called Biota. Biota is a layer of living species that covers our entire planet, of no more than 12-15 kilometers thick. This works as a living organism and we called it Gaia, in honor of the Goddess of the Earth (Gea-Gaya). (18) It is capable of regulating its temperature, concentration of oxygen and other parameters in order to maintain them stable, through inexplicable mechanisms. Here appears the environmentalist alarm about the risks of devastation of wooded areas, pollution of seas, alteration of atmosphere CO2 levels, which can modify the equilibrium as is now observed in the phenomenon of global warming.

Inflammatory response syndrome and mitochondrias

Endosymbiont theory, widely accepted today, acquired an unexpected significance to explain one of the mysteries in medicine, posttraumatic Inflammatory Response Syndrome.

Trauma frequently produces Inflammatory Response Syndrome (SIRS) similar to the one induced by sepsis. Bacteria release substances called PAMPs (Pathogen-associated molecular patterns) which activate immunocytes, and in trauma endogenous DAMPs (Damage-associated molecular patterns) are released. One of the mysteries regarding why the organism do not recognize these endogenous molecules as their own could be explained through the endosymbiont theory.

In a research published this year in Nature (19, 20),

the hypothesis that those endogenous molecules were the result of the release of mitochondrial material to circulation was evaluated. As mitochondrias are endosymbiont bacteria that maintain their ancient DNA, the release of that material would produce a similar response to the one of bacteria in infections. The authors confirmed that the circulating levels of mitochondrial DNA in patients who had suffered severe trauma were thousands of times greater, and could reproduce SIRS injecting their own liver mitochondrial material in rats. These mitochondrial DAMPs would be the responsible for the inflammatory activation in posttraumatic SIRS, with molecular similarity with bacterial activators of this response in sepsis.

CURRENT EPIDEMIC CHRONIC DISEASES FROM AN EVOLUTIONARY VIEW

There is a coincidence in explaining the current epidemic of obesity, diabetes, hypertension, and cardiovascular diseases due to the modification in diet and style of life mainly in the last centuries. The theory behind this explanation is the one of "thrifty gene theory or stingy". (21) In the book "El mono obeso", the author divides into four the nutritional stages of the evolution of hominids: the earthly paradise (50 million to 5 million of years ago), paradise expulsion two million years ago, carnivore by force 200000 years ago, and the current situation as The return to the diet Eden. (22)

The human race has developed throughout its evolutionary history against nutritional shortage, which facilitates the selection to a thrifty genetics of what was scarcer in nature, mainly sodium and fast sugars (only available in honey and some ripe fruits). The loss of the Eden of the wooded jungle led to look for resources in the capture of other animals, with great consequences, as the growth of the brain size, among others. As a common characteristic of carnivores, the low intake of sugar favors the brain sugar use over the muscular, producing muscular resistance to insulin. In diets rich in sugars and calories, muscular resistance to insulin becomes a pathogen mechanism related to obesity, displidemia and hypertension.

Evolutionary view helps us understanding our preferences regarding food preferences': our endorphins reward all what was scarce for long time and was difficult to obtain. In popular expression: we like all what is bad and fattening, that is to say, fast sugars, salty and fatty food; food industry is conscious about this. (23) Regarding the thrifty genes, advances in the evolutionary view on hypertension, obesity and diabetes have been developed.

Hypertension

The most indebted theory about the relation between salt and blood pressure, establishes a system of feedback where increases in salt consumption produce an increase in the levels of blood pressure, and induce to a greater excretion of sodium at kidney level. (24) In humans with very little salt consumption, in the context of "Paleolithic" diet, no progressive increase in systolic pressure with the age, normal in our culture, is observed. It is possible that one of the mechanisms of increase is attributable to the excess in salt of our diet: normal consumption of sodium in higher primates in their natural environment is of 0.5 grams/day, over 6-10 grams in our culture.

It has been observed that those African populations living in the United States, called Afro-Americans, have more sensitivity to salt in induction of blood pressure increase. (25) One hypothesis is that these populations lived for millenniums in areas with little availability of salt, making easier the selection to mechanisms "thirsty for salt", which take to greater elevation of blood pressure as a biological advantage in that context.

Another hypothesis is the one that relates hypertension in Afro-American population to the savage selection induced by slavery. (26) Slaves lived in overcrowding, with scarce food and frequent episodes of gastroenterocolitis that took them to dehydration and death. Under that circumstance the ability to save salt and elevate blood pressure could have been an evolutionary advantage associated with greater survival, which may explains the current behavior. The evaluation of the biological rationality of this theory is very complex, oriented to evaluate the prevalence of comparative genetic findings among the populations from Africa and the current Afro-Americans.

The obese monkey. Sarcopenic obesity

In an editorial letter, (27) Dr. Hernán Doval developed a detailed presentation about the nutritional anthropological theory as an explanation of the current diabetes epidemic, obesity, dislipemia, and hypertension. Based on researches of Elton et al. (28) it is observed that some of the investigated diets in archaeological sites of the Paleolithic era, before agriculture and ranching, were made of a 65% of fruits and vegetables, and meat was lean and with very little fat. Likewise, salt consumption was limited, similar to the current one in higher primates, as well as the sources of sugar of rapid metabolization. As a consequence of agriculture and food cooking, cereals were added; animal rearing involved the selection through rearing of species with greater capacity to accumulate fat, the availability of fast and refined sugars increased a lot, as well as salt in diets and the habit of drinking milk from other animals made a revolutionary change in diet and in the history of human diseases. With this change it is estimated that dozens of diseases were added to the frequent pathologies. (29)

In the last two centuries a massive immigration of the population to the cities, with the progressive abandonment of work involving physical effort, combined with greater availability of food resources

was produced. This situation has produced "sarcopenic obesity", related to a deep resistance to insulin due to the decrease of the body mass and abundance in food availability for large segments of the population is added.

EPIGENETIC, LOW BIRTH WEIGHT AND CARDIOVASCULAR RISK

Epigenetic concept and the possibility of inheritance of non genetic acquired characteristics

Human genome has only 30000 genes, and is almost identical to the chimpanzee. The difference in genetic expression is realized not only by the diversity of genes but its process of activation and control. There are multiple factors that "light" or "extinguish" specific areas of genes, modifying their expression, through several mechanisms called epigenetic. (30) The best examples of changes induced by epigenetic factors can be seen in the process of cellular differentiation of complex organisms. In the human organism all the cells have the same DNA, that is to say, their genes are identical. However, during embryonic development cells are differentiated, and in adult parenchymas when one kidney or liver cell is reproduced produce only cells of their lineage, due to epigenetic control.

The most exciting about this topic is that epigenetic factors may be influenced by early experiences during the development or the first years of life and epigenetic modification may be in some cases added to reproductive cells and transmitted in inheritance. In a very commented editorial is stated that descendants can inherit "sins of the fathers, and their fathers". (31)

In an intellectual experiment proposed by Jablonka et al. to understand this control, a group of scientists disembark in a planet and discover non complex ways of lives but different among them. When investigating their DNA they found that all of them share an identical sequence. They suspect that life came to that planet in a meteorite with only one species and in conditions that did not allow DNA mutation. The influence of conditions in the new planet makes possible to imagine a great variety of independent forms of life than sharing the same DNA could had been adapted by epigenetic mechanisms. Forms could be as different as the diversity of cells in the human body. In their book four ways for evolution are studied: genetic, epigenetic, behavioral and symbolic, with a really exceptional technique. (32)

Epigenetic and cardiovascular disease

The association of low birth weight over the risk of cardiovascular diseases in adult life an even in descendants have been studied through epigenetic. (33, 34)

One of the explanations of this phenomenon is the possibility that nutritional disorders during pregnancy leave an epigenetic stamp which can modify in a sustained way the epigenetic activity in adult life and also can be transmitted by inheritance. From the evolutionary view, malnourished fetus is biologically prepared for a context with little food, increasing the expression of thrifty genes. This has been observed in the animal experimentation in the so called fetus programming of hypertension, and an exceptional circumstance made possible its study in humans.

In the winter of 1944-1945, German occupants subjected Holland to a food rationing that resulted in a situation of famine, known as Dutch Hunger Winter. Health records were maintained so years later it was possible to analyze the effects of hunger in pregnant women over their descendants. The Dutch Famine Birth Cohort Study (35, 36) demonstrated that hunger during pregnancy is associated with a greater incidence of unfavorable lipid profile, coagulation disorders, greater obesity when adults and triples the incidence of heart failure at age 50. One of the explanations is that through biological adaptive mechanisms hunger during pregnancy produces a sustained modification of metabolic patterns. This hypothesis was confirmed through the analysis of epigenetic differences in the control of IGF 2 (insuline-like growth factor). Six months after famine, those persons that suffered hunger during their three months pregnancy had lower methylation of IGF 2 gen than those that suffered hunger during their last three-month pregnancy or brothers born after that period. (37)

Hypertension is associated with genetic and environmental factors, but an epigenetic influence has also been demonstrated. In the so called fetal programming, hypertension in adult rats is induced through different situations which results in intrauterine stress. As we have already commented, in the natural experiment of the Dutch famine, this alteration produces an epigenetic memory which is maintained until adulthood. In rats' model, the administration of Angiotensin-converting enzyme inhibitors during pregnancy prevents the development of hypertension in adulthood. The apparent substrate is the expression of the adrenal AT1b Angiotensin receptor that can be methylated in a greater or lesser extent depending on stress and administration of inhibitors. Although this has not been explored in humans, scientists consider that can be one of the explanations with more tendency to the development of hypertension associated with maternal stress. (38)

As a general comment, during fetal life different factors have incidence on genetic activity which would be perpetuated during life and eventually be transmitted to descendants.

HEART FAILURE AND NEUROHUMORAL ACTIVATION

In patients with heart failure the organism tends to retains water and salt, activating the renin-angiotensin aldosterone system. Levels of circulating catecholamines and neuroadrenergic stimulation are increased. This process is harmful, and all the medication that has demonstrated prolonging life in patients with heart failure is focus on antagonizing

it: converting enzyme inhibitors, antialdosteronics, beta-blockers, and diuretics. From the evolutionary point of view is understood that these are mechanisms activated for secondary tissue hypoperfusion to the traumatic blood loss, frequently in nature and in these mechanisms maintaining adequate levels of hypertension and saving salt and water lost gives advantage on survival. (39)

BIOLOGICAL SELECTION AND EMOTIONS. A RESEARCH IN ORDER TO EXPLORE THE RELATION BETWEEN NEGATIVE EMOTIONS AND ACUTE CORONARY SYNDROME

From the evolutionary approach the exploration of emotional aspects has the risk to lead to organicism to explain moods or to reductionism to explain social behaviour due to genetic terms. Emotions are real programmes for action that have been biologically selected. In cardiology, the diffusion of stress concept as an unspecific reaction to different emotional or extreme contextual situations has debilitated the access to reading the great literature published in the last decades about biology of specific emotions, both in humans and animals. In 1983, in the first publications of Paul Ekman et al. in the Science journal (40), while analyzing the behaviour against different emotions of the autonomic activity, the distribution of blood flows in different organs or parts of the body, heart rate, blood pressure and skin temperature in hands, allowed the distinction between diverse emotions as anger, fear and sadness.

There are not biologically identical, anger and fear, as well as sadness and disgust, among other emotions.

From the biological point of view, emotions are very specific. Each emotion can be defined with enough precision, at least those called simple. It would be impossible to conceive emotions if we cannot distinguish them biologically, denying its evolutionary biological sense. The emotion is a stereotypical response that synchronizes different areas of the organism and that has been phylogenetically selected because it anticipates mechanisms that give advantages to endure the situation interpreted as imminent. This response can be triggered against characteristic stimulus that have a genetic root or against learnt symbolic or cultural phenomena both in humans and mammals.

The best studied emotion is fear due to the ease of inducing it in all species. (41) As it happens in the kingdom of mammals, human beings facing a threat situation answer with stereotypical responses, with greater or lesser intensity according to the magnitude of the stimulus and our predisposition: initial immobility, pale face and hands, flow increase in lower limbs, decrease flow to hands (upper limbs), piloerection, tendency to diuresis and cataract, increase of pain tolerance and scary face. Darwin was surprised of the evolutionary persistence of piloerection behaviour, which involves simultaneous contraction of tens of thousands of small muscles throughout the body and that can be looked as a fear reaction even in fish. (42) In the table there are summarized the evolutionary advantages of each of these mechanisms. (Table 1)

It is clear that today feeling abdominal colics or cold hands before and exam does not provide any evolutionary advantage, except to understand that we live in an emotional universe essentially metaphorical. The ravage we have in the exam is biologically faced as the possible attack of a predator.

It is documented that each physiopathologic

Table 1. Evolutionary advantages of fear reaction

Biological component	Advantage for survival
Immobilization	Decreases the signal to the predator that awaits.
Skin paleness and coldness	Decreases the thermal emission to the predator.
Increase of flow to lower limbs	Preparation for flight.
Piloerection	Increase of body size that has a threatening role on the predator.
Tendency to diuresis and cataract	Confusion of smells that guide the predator.
Increase of pain tolerance	Even if he is injured, he would escape.
Scary face	To communicate to his community the danger situation. Fear is contagious as every intense emotion.

Table 2. Metaphoric hypothesis of the multiple pathogenic mechanisms activated in patients with acute coronary syndrome. (47)

Activated mechanism	Objective	Interpretation	Cause Information:
Prothrombosis	Avoid blood loss	Bleeding wound	Existence of a severe area
Increase of platelet aggregation	Repair endothelial lesion	Endothelial wound	Cardiac or imminent suffering
Inflammatory activation	Answer to the aggression	Aggression-threat	It must be excluded
Vasoconstriction	Close territory- avoid flow	Inconvenient flow	Painful area- wound

component of acute ischemic heart disease (vasoconstriction, protrombosis, platelet pro-aggregating, inflammation) can be promoted by negative emotions. (43) As an example, in patients with infarctions related to emotional situations, a particular response of increase in the level of circulating platelets facing a simple stress (exercise of speaking in public) has been observed, not observed in patients with no emotional factor despite an identical modification in blood pressure and heart rate. (44)

In a risky proposal I have tried out an interpretation that can relate degradation and public shame situations in patients with infarctions (45, 46) to the confluence of mechanisms that are simultaneously activated, as it occurs in every emotion. This response has sense if we assume metaphorically the intense suffering of that negative emotion as a threat or a broken heart. (Table 2)

We are working in a research protocol that in some years would indicate if this hypothesis has scientific support. It has the advantage that can be explored in adequate models, which perhaps can be better understood from an evolutionary view.

CONCLUSIONS

I have summarized some examples in frequent pathologies or associated with the cardiovascular system, but evolutionary thinking has studied diverse areas of medicine: backache, the ideal position to sleep in children, depression and suicide, hyperbilirrubinemia of the newborn, cancer, infections, bacterial resistance, etc. To try a better education in the subject, there are several books of general nature (48, 49) and also specific sites in English and Spanish. (50)

In the last ten years proposals to consider the teaching of evolution as a relevant subject in the biological education in students of medicine have been multiplied. Oxford's medicine book has added to its 2010 edition a chapter about the evolutionary view of medicine (51), and some universities have already added to their curriculum. Evolutionary and functional reflection of the physiopathologic mechanisms adds an enriching dimension, allowing the elaboration of hypothesis that can be explored with the new genetic techniques.

Carlos Daniel Tajer, M.D.
Director of the *Argentine Journal of Cardiology*

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