The Role of Mitochondria and mit-DNA in Oncogenesis

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ABSTRACT

Mit-DNA is mainly responsible for cell respiration in biological systems, and the genetic alteration of mit-DNA affects mitochondrial activity. It will be here analyzed a well defined mitochondrial cytopathy which is connected, from the moment of birth, with several inherited diseases, such as cancer. The chance to investigate, indirectly and through bed-side evaluation, mitochondria functionality opens new ways to understand and face the very beginning states of the process of oncogenesis, giving original impulses to diagnosis and prevention. Finally, a multidisciplinary and integrated approach involving biology, physics, mathematics, chemistry, philosophy, etc. opens new perspectives both for classical and social sciences.

Introduction

This paper highlights the central role of mitochondria and mitochondrial DNA (mit-DNA) in the process that underlies the transformation of a healthy cell into a cancer cell. For this purpose it is useful the Quantum Biophysics Semeiotics - QBS, extension of the classical semiotics with the support of quantum and complexity theories, a scientific approach first described by Stagnaro et al. (Manzelli, 2007b) based on the Congenital Acidosic Enzymo-Metabolic Histangiopathy – CAEMH (Stagnaro, 1985), a unique mitochondrial cytopathy, present at birth and subject to medical therapy.

We will see how chaos theory, quantum theory, and concepts such as synchronicity, entanglement, strange attractors, non-local reality, energy-information and DNA "antenna" defined by Manzelli (2007), are crucial for understanding the diagnosis, prevention and therapy of tumors, and especially to reveal the Oncological Terrain (Stagnaro, 2004a). The autopoietic theory (Varela, 1974) will be a useful key-tool to interpret the behavior of biological systems here analyzed.

According to the research of Stagnaro, today the doctors should be able to evaluate, at the bedside of their patients, simply using the stethoscope (Stagnaro, 1978), mitochondria functionality, as well as the functionality of all biological systems. It is now possible, from the moment of birth, to make a diagnosis in order to detect the presence of Oncological Terrain linked, whether or not, with Oncological Congenital Real Risk (Stagnaro, 2009), so that an intelligent prevention strategy can be implemented only on those subjects with Real Risk, without incurring additional costs for the NHS[1]. The prevention done on the basis of QBS constitutions - i.e. Coronary Artery Disease – CAD (Caramel, 2010), Oncological Terrain, Diabetics Constitution (Stagnaro, 2004c), etc. - will prevent the onset of the more serious diseases that humans suffer from today - for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction.

1. State of the art

Genetics, chaos and fractals

"A complete set of genes of an organism, namely its genome, has a huge interconnected network, rich in feedback loops, in which genes regulate each other's actions directly or indirectly. The genome is not a linear series of independent genes (characters) but rather a tightly woven network of reciprocal effects mediated by multiple repressors and de-repressors, exons and introns, jumping genes, as well as structural proteins." (Francisco Varela)

Several works of the last decades evidence the importance of deterministic chaos and fractals in genetics. The research of Kauffman (1993), using binary networks in cellular automata, shows that the genome can be represented with a binary network at the edge of deterministic chaos, or by a network with a frozen core and islands separated from variable nodes. This is a plausible model of evolution and adaptation that has been proved correct. By studying the complexity of biological systems, the focus has shifted from the structures to the processes that 'emerge' from them. In the past there was the view of genes as stable and clearly distinct units that transmit hereditary characteristics. Genetic stability is instead an emergent property that stems from the complex dynamics of the whole cellular network. The stability of genetic structure is the result of a well-orchestrated dynamic process that requires the participation of a large number of enzymes, organized in complex metabolic networks that regulate and ensure both the stability of DNA molecules, and the accuracy of their duplication. During duplication the cell not only passes the double helix newly replicated DNA but also a complete set of enzymes, coenzymes and ions needed for metabolic processes such as membranes and other cellular structures: in short the entire cell's network. In this way, cellular metabolism can perpetuate itself without ever leaving the pattern of their self-generated networks.

In all living organisms there is a subtle balance between genetic stability and mutability; the ability of the organism to actively produce mutations is only acceptable if it helps evolution. The regulatory mechanisms of mutability show a growing abundance of details. The mutations, actively generated and regulated by epigenetic cell network, and evolution are an integral part of self-organization of living organisms. The stability of genes is therefore not an intrinsic property of DNA molecules, but a result of the complex dynamics of cellular processes.

Keller discovered that the signal (or signals) that determine the specific order or pattern to which DNA must conform after recombination as a result of the final transcription process comes from those regulating complex dynamics belonging to the cell in its wholeness (Capra, 1992). From the dynamics regulating the cellular network can emerge many different proteins from a single gene, and a single protein can develop multiple functions. If we shift our attention from a single gene to the entire genome, there are many other problems that cast doubt on the idea of genetic determinism. For example, when a cell divides during development of an embryo, each new cell receives exactly the same number of genes, but these cells then take on very different skills (muscle cells, blood, nerve, etc.). The types of cells do not differ from each other with regard to the genes they contain, but for those in each of them are actually being active in the presence of different mitochondrial kit. Genes do not act on their own behalf, but must be activated. For example, Monod et al. (1961) introduced a theory: a distinction between structural genes that encode proteins and regulatory genes that control DNA transcription and thereby regulate gene expression.

Recent research has revealed the fractal structure of the cytoplasm (Aon, 1994), of the genome (Dekker, 2009) and the chance that the electron can be represented with the typical complexity of a strange or chaotic attractor (Horwitz, 2004).

What emerges from these studies is the deeper understanding that biological processes involving genes are all regulated by the cellular network in which the genome is integrated. This network is a highly non-linear reality, a reality that contains multiple chains of feedback, so that patterns of genetic activity change constantly in response to changing circumstances. DNA, although certainly being an essential part of the epigenetic network, is not the only causative agent of forms and biological functions, as stated in the central dogma. The form and biological functioning are emergent properties of nonlinear dynamics of the network and we expect that our understanding of these processes of emergence will increase significantly with the application of chaos theory to the new discipline of epigenetics. Recent experiments in genetics have shown that the loss of individual genes - even when they thought they were essential - has very limited effects on the functioning of the body (Capra, 1997). Under this remarkable stability and robustness of biological development, an embryo may be different from the initial stages - for example in case of individual genes or whole cells are accidentally destroyed - then still reach the same mature form that characterizes the species to which belongs.

Natural selection does not operate on individual genes but on the scheme of self-organization bodies. It is possible to represent the whole process of biological evolution as a trajectory in a phase space that moves within a basin of attraction to an attractor (Medio,

1992) that describes the functioning of the body in the stable form that characterizes his adulthood. Complex systems exhibit nonlinear structural stability. A basin of attraction can be distorted or disturbed without changing the fundamental characteristics of the system. In the case of an embryo during evolution, it means that it is possible to change, to some extent, the initial conditions of the process without seriously damaging the development of the whole organism. Therefore, the stability of development, which remains a mystery from the perspective of genetic determinism, is clearly a consequence of basic properties of complex nonlinear systems.

Mitochondria and mit-DNA

DNA mutation and recombination are the two main way of bacterial evolution, but Margulis (1993) discovered a third way: the symbiosis. The most remarkable evidence of evolution through symbiosis - the tendency of different organisms to live in close association with each other, as the bacteria in our gut - is offered by mitochondria[2], the power plants that are found within most nucleated cells.

Margulis believes that mitochondria were originally bacteria floating freely. In ancient times these bacteria invaded other microorganisms so they first settled in them. These bodies fused together then evolved into more complex life forms, breathing oxygen. There was therefore, in this case a more abrupt evolutionary mechanism of mutation: a symbiotic alliance that became permanent.

These fundamental components of all animal and plant cells that perform cellular respiration, contain their own genetic material and reproduce independently and at different times than the rest of the cell, and in fact have their own DNA, mitochondrial DNA[3]. In the cell there are therefore two DNA: nuclear DNA (n-DNA) and mitochondrial DNA (mit-DNA), and parallel to the nuclear genome there is mitochondrial genome. Men and women inherit the mitochondrial genetic code almost entirely from the mother: this is because the mitochondria in the sperm are present only in the tail, which does not enter the oocyte.

In mitochondria a relative abundance of inorganic ions, potassium, magnesium and phosphate is present plus in mit-DNA, cytosine and guanine content is higher than in n-DNA. Indeed, part of the mitochondrial proteins are synthesized within the mitochondrion itself, under the control of its mit-DNA, which replicates autonomously, since it contains the necessary information - a particular genetic code - for the synthesis the inner mitochondrial membrane enzymes. Mutations and alterations in mit-DNA occur six to seven times more than in n-DNA, presumably due to the lack of protective histones in mitochondria and because of the fact that the mit-DNA is closer to the electron transport chain, exposing high concentrations of free radicals, which can damage the nucleotides. Furthermore, in mitochondria the DNA repair mechanisms are lacking, so that mutations in tRNA, rRNA, and in the transcription of proteins are more frequent than in the rest of the cell. The basic elements to build DNA, RNA and enzymes, the power's vectors which supply each one of the above mentioned processes, are given by the mitochondrial activity.

Autopoiesis and Energy Information

Deterministic chaos has been defined from the Royal Society of London in 1986 as the 'stochastic or probabilistic behavior occurring in a deterministic system' and its main characteristics are the uncertainty and unpredictability, but it is possible to detect and investigate it and to get qualitative information through invariant statistic measures such as LCE[4], fractal dimension[5] and entropy[6] (Medio, 1992). Entropy represents the rate of uncertainty, or equivalently, the rate of variation of qualitative information of dynamical systems, and is strictly related to LCE.

The importance of the quality of information in deterministic dynamical systems is evident in the causal interpretation of quantum theory (Bohm, 1980), which supposed the electron, or any other elementary particle, to be a certain kind of particle which follows a causally determined trajectory[7]. In addition to the Newtonian classical potential, the particle[8] moves according to a new potential, called Quantum Potential – QP – which is determined by the quantum wave field[9], or wave function. QP is independent of the strength, or intensity, of the quantum field but depends only on its form, so that the information in the form[10] of the quantum wave directs the energy of the electron and even distant features of the environment can effect this movement in a deep way.

The feature, in which very distant events can have a strong influence, is what is meant by a nonlocal interaction. Non-locality implies an instantaneous connection between distant events and does operate in nature, as proved by Aspect et al. (1982), who provided strong evidence for a nonlocal form of interaction. This result follows in a natural way, within the causal interpretation, as a result of the nonlocal QP that directly connects distant particles.

Sub-quantum behaviors and biological systems dynamics are usually considered as separated and different worlds, but there are some interesting works as recent findings of large scale quantum coherent effects associated with photosynthesis (Collini, 2010), and Lory's experiment (Stagnaro, 2008) that open new perspectives about the presence of non-local reality in biological systems.

Furthermore, since life system is based on the communication system, DNA functioning can not only be seen as a storage of genetic information. We can consider DNA/RNA dynamic system as an Information Energy (EI) catalyst (Manzelli, 2009) able to transmit and receive bio-physical quantum signals to and from the proteins in the living cells, so DNA can be thought as an "antenna" transmitting nonlocal information[11] through 'gene quantum signals'.

All events in nature belong to a particular form of different codified energy transmissions, so that the total energy can not be created or destroyed. Manzelli argues that information is a kind of a virtual energy as a pure qualitative entity, and EI is a part of the total energy–matter transformation. The variation of the sum of all the transformations of energy, Vibration Energy (EV) codified Energy like Matter (EM) and Information Energy (EI) must always be equal to zero at any time[12].

According to the causal interpretation of quantum theory, Bohm (1980) introduced the idea of implicate order, a particular kind of hidden enfolded order that guides the

explicate order, which corresponds to a world view in which the basic notion is one of separate objects moving on trajectories in Cartesian coordinates, through a dual movement of enfoldment and unfoldment called holomovement[13].

The whole implicate order is present at any moment, in such a way that the entire structure growing out this implicate order can be described without giving any primary role to time. Particles are no longer considered as autonomous and separately existent: everything implicate everything in an order of undivided wholeness. Structure is basically dynamic (Bohm, 1989), so the deeper question is that of how this structure originates, how it grows, how is sustained and how it finally dissolves. The act of structuring leads to relatively stable products of this process called structures. Any structure is subject to a process of organization and disorganization.

In biology, Varela et al. (1974) proposed the theory of autopoiesis, useful to understand the connection between organization and structures in living systems. An autopoietic system, so as described by Maturana and Varela, is based on a scheme of autopoietic organization through a process of structuring which can lead to different structures. A recent work (Davia, 2006) connects autopoiesis, fractals, catalysis and dynamic systems.

The autopoietic organization is conservative and always acts on itself: self-production, self-regulation, self-referential, recursion, circularity. The scheme of organization works relentlessly to achieve the autopoiesis through a continuous process of structuring, generating dissipative structures with non-linear dynamics (Prigogine, 1967).

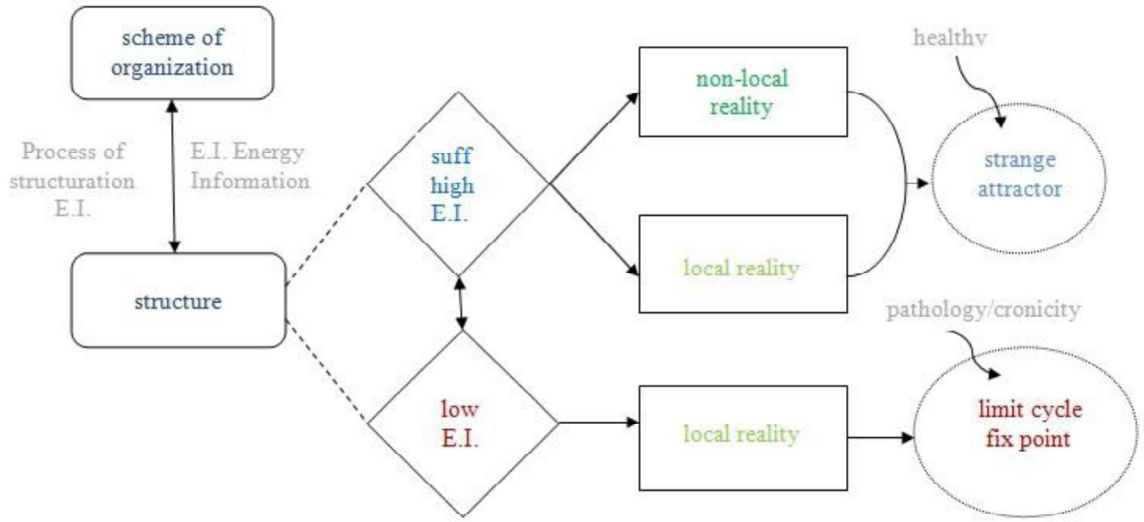
An autopoietic dissipative structure, always acts satisfying (or trying to meet) the autopoiesis in a simultaneous and synchronous way: there is no cause and effect, but a-causality in a timeless dimension (Capra, 1997). An autopoietic system is autonomous so that it does not depend on time. This is enough to justify the behavior of living autopoietic biological systems, where there is simultaneity and synchronicity, indices of a no-local reality.

There is structural coupling between organization (conservative) and structure (dissipative) to achieve always the autopoiesis. For example, if there was a tendency to disease in biological systems (or if there is pathology), the organization – i.e., the PNEI, psycho-neuro-endocrine-immunological system, would always be orientated towards the survival, materializing and engaging compensatory mechanisms to restore the simultaneity and synchronicity.

In the following chapters we will verify and test in biological systems the hypothesis of the correlation between nonlocal reality and deterministic chaos, of the co-presence of local reality and non-local reality in physiological states, and of a sufficient high amount of information energy (EI) as catalytic process to maintain no-locality in the autopoiesis.

In the autopoietic living biological system (e.g., nervous system, immune system), if there was a disease, the autopoiesis would still function. The organization would remain intact, it is stable, continuous, always on, it is a conservative system, and if there were not, the structure and the system would disintegrate, it would disappear the life itself! In macro-interacting biological systems there is a "mind" synthesis of an autopoietic system that is based on a composite unit (e.g., psycho-neuro-endocrine-immune system).

If the system was fully healthy, there would be actually a non-local reality (parallel to the local reality) - simultaneity and synchronicity - and the presence of deterministic chaos (chaotic or strange attractor). If there was disease, the autopoiesis would still be present, but the non-local reality and the correlated strange attractor equilibria, corroborating the presence of deterministic chaos, would disappear so that we would observe just limit cycle equilibria in the case of pathology, and fixed points in case of chronicity. The presence of just the local reality is a consequence of the reduction of EV and EI, but with proportional increase of EM[14].



Scheme 1. Autopoiesis and Energy Information

In autopoiesis there is learning, compensation, adaptability, change, self-adjusting, updating and continuous renewal, moment by moment: these are typical characteristics of dynamical systems with chaotic behavior, where there is sensitive dependence on initial conditions (SDIC). There may be shocks and disturbances, then it needs receptivity, sensitivity, constant and continuous attention: there are no breaks in life (God help us if the heart stopped beating and if we cease to breathe!). Learning takes place as a timeless process of transformation. In emergency situations (transient or permanent) there is re-structuring and in it there is a continuous and synchronous simultaneous action, moment by moment, but to our eyes it appears as a succession of events "cause and effect" included in our space-time coding (e.g. transmission of information in space-time). The re-structuring has the character of simultaneity and discontinuity, all the time. The process of materialization/structuration from organization to structure is updated constantly, in a simultaneous and synchronous way.

In the study of nonlinear dynamical systems the chaotic attractor is different, moment by moment, because are changing initial conditions. If the attractor "collapses" to limit cycle, there is a reduction of complexity, there is a reduction of entropy[15], there is loss of quality and information. Each configuration of the strange attractor (we observe it in non-local reality) is not dependent on the previous configuration, it does not depend on the past, but only on the specific set of initial conditions that characterizes it at that particular moment. The structural coupling is born and dies every moment in a constantly

updated changing in accordance with autopoiesis (conservative organization) and quantum and dissipative behavior of their structures, at least in biological systems (Manzelli, 2007b). The sequential transformation that we observe "looking" gradually into a strange attractor transforming itself in a limit cycle is illusory, as is the movement of waves on the sea surface. The space-time dependency, in this case, is a projection of our world, which we generate according to our perceptions, beliefs and ability to see.

Most of metabolic processes are facilitated (catalyzed) by enzymes and receive energy through special molecules known as organic phosphate or ATP, of mitochondrial origin. All cellular structures exist in conditions far from thermodynamic equilibrium: they are dissipative, far from equilibrium with their own stability, spontaneous emergence of new forms of order. As the flow of energy increases it is possible that the system encounters an instability - fork - at which the system itself can enter into a completely new state, where new structures and new forms of order can emerge - emergences - or self-organization (Prigogine, 1967).

Creativity is a key property of all living systems, and if cell metabolism does not use a constant flow of energy to repair structures as soon as they damaged, quickly they would decay to steady-state: the cell would die (from chaotic attractor to limit cycle to fixed point). If it is reduced the blood flow in an artery, the microcirculation would activate itself, but the fractal dimension would be reduced. We then describe the cell as an open system. Living systems are closed at the level of organizational structure (they are autopoietic networks), but open in terms of materials and energy. "*The cell enter in connection automatically with other bodies. If it expels something, there will be any other body that will absorb it*" (Lynn Margulis)

Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH)

Cytopathy is the state of suffering of cells, which associated with mitochondria and alterations of mit-DNA, is indicative of diseases in humans, often only potential, as in the biophysical semeiotic constitutions and its related inherited congenital Real Risks (Stagnaro, 2004a). It has been identified several syndromes associated with specific mutations and alterations in mit-DNA, associated with mitochondrial cytopathy, such as cardiomyopathy, hypoglycemia, diabetes, respiratory problems, epilepsy and stroke.

Stagnaro (1985) defines a well determined mitochondrial cytopathy, pathology called *Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH).* CAEMH is called CAEMH-α in his most intensive form, which has got a key role in the semeiotic biophysics, in the clinical microangiology and in the modern medicine.

There is general agreement among the authors in finding that mit-DNA is phylogenetically related to blight's one, morphologically and functionally resembling with it, and that, during the long endosymbiosis, the mitochondria have lost some genes (Morgan-Huges 1982, Wallace 1987). Commonly understood, the majority of human genes is located in the nucleus and are transmitted equally from both parents to offspring. However, there is a series of essential genes located in mitochondria, relatively autonomous bodies in the cell (Shaw, 1988), transmitted to the offspring "almost"

exclusively maternally, since only a few mitochondria and a small quantity of mit-DNA are present in human sperm. Thus, the enormous superiority of the female mitochondrial heritage could be better on the few male mitochondria "crushing" them, but it is likely that this does not happen only, because it has never been shown to contain molecules derived from mitochondrial father in the offspring of mammals (Wallace, 1985).

The problem of matrilineal transmission is still not completely resolved and, on the other hand, there are rare cases of mitochondrial diseases transmitted surely via paternal. We agree with this statement, as it looks - although rarely - the presence of CAEMH in sons or daughters of parents, where only the father was a carrier of functional mitochondrial cytopathy described so far.

Clinical evidence has enabled the observation that mit-DNA and n-DNA from both parents interact between themselves and with environmental factors determining the phenotype (Stagnaro, 2004a). It appears extremely interesting and currently we can not refute the fact that positive mothers for the Oncological Terrain (Stagnaro, 2009a) or affected from one of the several semeiotic-biophysics constitutions[16] give birth to sons (and daughters) carrying the same constitution.

However, if the children are "physically" like the father who is "negative" for this or other pathological predispositions, in 50% of cases these children do not have those constitutions, and this fact demonstrates the interaction between genes both on the mit-DNA and on the n-DNA of "both" parents.

On April 11, 2010 Stagnaro announced the first case in the world of a newborn without Oncological Terrain (OT), born from parents both positive for OT, but in the "residual" variant thanks to a treatment through a proper diet and melatonin[17] (Stagnaro, 2010). This event will radically affect the primary prevention of cancer as witnessed at the site of the "Los Angeles Times" on April 11, 2010[18].

The mitochondrial genes, given their particular location, code for the synthesis of essential components of the system of energy production: the 120 watts of power, needed for daily energy needs of the human body, are provided mostly by mitochondria. To what was previously mentioned, it is clear that the mitochondria play an important role, independent from the nucleus in the transmission of certain genetic characteristics and that the inheritance transmitted diseases with mit-DNA may not follow the Mendel's laws (Rosing 1985, Walter 1981, Luft 1962).

In recent years many researchers have turned their attention to the so-called "mitochondrial cytopathy". While some of these conditions are characterized by alteration of oxidative-phosphorylation's pathway[19], in others it is compromised the entry of substrates with high chemical energy inside the mitochondria or the ability to generate reducing potentials from these substances. The clinical phenomenology of mitochondrial diseases, still looking for a specific classification, depends on the site and intensity of the alteration as well as the type of tissue. Particularly vulnerable are the cardiac and skeletal muscle, brain and retina due to their intense aerobic metabolism and the need for large amounts of ATP (Gadaleta, 1986). As demonstrated in clinical and epidemiological evidence, there are several types of "mitochondrial cytopathy", of various kinds and severity, with no clinical phenomenology, at least in milder and/or youth forms.

Following these considerations, in the 70s Stagnaro assumes the existence of a functional mitochondrial disease, which affects primarily tissues with high aerobic metabolism and can cause, in its most intense form, metabolic disorders, perhaps under the negative influence of environmental known or unknown factors (Stagnaro, 1981). This mitochondrial cytopathy function was considered clinical, the "genotype" or *conditio sine qua non* of the most serious human diseases as a result of reduced ATP production and subsequent impairment of essential cellular functions: domestic work and other activities necessary for organismic economy, typical of a "social element", as is the configuration of a normal cell. Furthermore, it is interesting to evidence the impairment of vascular smooth muscle cells, a distribution district, by this "mitochondrial cytopathy" which comprehensively explains the complex changes in the tine microcirculatory "game", cause of the histangical local suffering[20].

The *functional mitochondrial pathology* (Stagnaro, 1985) is called *Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH)*, descriptive concept to highlight the main characteristics of mitochondrial cytopathy. CAEMH is characterized by numerous biophysical semeiotic signs of the *right cerebral dominance*, more precisely, of the right Planum temporale prevalence. The easier signs to detect are the following:

1) cerebral gastric aspecific reflex is more intense when trigger-point of right hemisphere are stimulated by digital pressure of "mean" intensity, indicating the typical right cerebral dominance (Stagnaro, 2004a): latency time 6 sec. *versus* 7 sec. when digital pressure is applied on trigger-points of left cerebral hemisphere; moreover, the intensity appears to be 2 cm ca. *versus* 1,5 cm (Fig.1);

2) cerebral evoked potentials (digital pressure of mean intensity on leg or arm, right and then left, while doctor evaluates cerebral-gastric apecific reflex) show Lt (latency time) lower when assessed at level of right cerebral hemisphere: Lt 6 sec. *versus* 7 sec., during digital stimulation of left arm trigger-points;

3) v*asomotility* and *vasomotion (*fluctuations of reflexes) in the right hemisphere are more intense than those in the left one. Due to the lack of reader's biophysical semeiotic knowledge, it is sufficient to know that doctor evaluates this particular situation, related to cerebral microcirculatory chaotic-deterministic fluctuations, by way of urethral reflexes oscillations: superior urethral reflex (v*asomotility*) and inferior urethral reflex (*vasomotion*)[21].

Since its discovery, it has been noted that CAEMH is characterized by *cerebral asymmetry* due to right cerebral dominance, more exactly said, by prevalence of *right Planum temporale*, notoriously located between Heschel convolution (*gyrus)* and posterior segment of Silvio's fissure.

CAEMH-α[22] is a functional mitochondrial cytopathy, characterized by a congenital mitochondrial respiratory alteration, genetically directed, generally but not exclusively (93%) inherited through the mother, which compromises the activity of mitochondrial respiratory chain in an important way. In fact *enzymatic dysfunction* in the breath chain, and as consequence metabolic mistakes provoke a reduced level of intracellular free energy and histangical acidosis, and it is different in intensity from tissue to tissue as well as from part to part of the same tissue. The remains 7% is inherited through the father, because

mitochondrial genes encode only 13 sub-unities of 5 complexes of the respiratory chain, while the remaining one is directed by nuclear genes.

From a clinical point of view, CAEMH-α, characterized by the presence of cerebral right asymmetry, due to the prevalence of the right cerebral "*Planum temporale*", is, without any doubt, the most interesting form.

'Semeiotics' can easily recognize and 'Biophysics' "quantizes" the CAEMH-α: the cerebral-gastric aspecific reflex, as reported above[23], is much more intense (2 cm versus 1,5 cm) when the pressure is digital or manual applied to the trigger-points of the right hemisphere (frontal region, temporal, parietal, occipital, eyeball, etc.) and the Lt (latency time), on the right side, is 6 seconds, while on the left side is 7 seconds (different histangic pH). Very interesting is the evaluation of different parameters from a "dynamic" point of view: for example, by inviting the subject to be examined to "think" or make "mental" math: the brain-gastric aspecific reflex shows a reduced latency time (5 seconds on the right side, and 6 seconds on the left side) and the difference in intensity is statistically enhanced in a significant way.

There are various forms of CAEMH, however, the only worthy of consideration in practice and research is the CAEMH-α, characterized by an intense gastric aspecific reflex (> 1 cm approximately) even during digital pressure exerted on the lower third of skeletal muscle, where oxidative metabolism is more efficient and high, cause of evolutionary nature.

Latency time (Lt) and intensity of this reflection (and others who are not interested at the moment) are linked directly to tissue pH and, therefore, to the degree of free hydrogen ions, depending on the actual intracellular energy level. Digital pressure turns the affected tissue in a thermodynamically isolated system, where the free energy at this time, i.e., in basal conditions with the subject to be examined supine and psycho-physically relaxed, is consumed in a much shorter time as less than usual is the content of nucleotides phosphorylated with potential high energy.

Moreover, the intensity of acidosis so achieved, always correlated with the level of intracellular energy base, is much greater, at the same elapsed time from the beginning of tissue pressure, as is compromised mitochondrial respiratory function, i.e. as appears impaired the oxidative phosphorylation. What just said is corroborated from simple experimental evidence: Lt of digital fingertip reflex during medium[24] intensity pressure, in healthy is 5 seconds. If the subject performs the apnea test (no breathing for approximately 10 seconds)[25], the latency time is reduced gradually, but just after 10 sec. from the beginning of the test, because the microcirculatory activation type I, associated, caused by apnea, physiologically fully compensates the low intake of matter-energy-information to the parenchyma within about the first 10 seconds.

At this point it should be noted that the dietary therapy, etymologically understood, and administration of histangic-protectors positively change the cellular respiratory activity leading to increased intracellular free energy and the improvement of the parameters of the several semeiotic-biophysical signs revealing CAEMH-α, which, however, does not disappear altogether.

Experimental and clinical evidences of the "existence" of CAEMH

The clinical and experimental evidence that corroborates the "existence" and the clinical significance of CAEMH are as numerous as resistant to any attempt of forgery.

They show that as a result of alteration – slow or stop - the flow of matter-energy-information in mitochondria, in accordance with the exemplary methodology proposed by Dioguardi and Di Padova. Red-ox mitochondrial processes are being undermined, thereby with occurrence of tissue acidosis, because of biophysical-semiotic phenomenology described above. In fact, Gastric aspecific reflex "vagal" – caecal, urethral - and spleen decongestion during "medium" intensity digital pressure on any biological system or on its projection on the skin - more specifically, on its related trigger-points, particularly the cerebral hemispheres, with the parameters outlined above (Fig. 1).

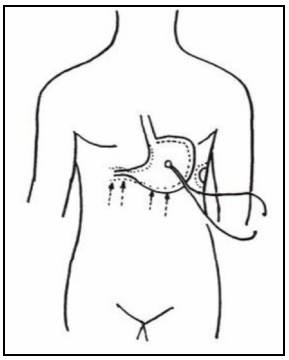


Figure 1: Auscultatory-percussion syndrome of CAEMH. Both gastric aspecific reflex, "vagal" type, and spleen decongestion, indicating the presence and pointing out the intensity of CAEMH

Experimental evidences of the "existence" of CAEMH

A) In a healthy young subject, supine and psycho-physically relaxed, strictly applied a tourniquet around an arm or a leg to block the arterial flow in the brachial or femoral artery (tourniquet test), transforms tissues downstream in a biological system (almost) thermodynamically isolated, where the normal restraints of entropy cease: glycolysis from "aerobic" becomes "anaerobic", with local accumulation of lactic acid, H^+, CO_2, and thus it increases the activity of hydrogen ions ($\downarrow$ pH). At this very moment of "critical" acidosis, no longer matched, applying digital pressure over the tissue downstream from the site of tourniquet, where the O_2 is no longer the reducible substrate that can oxidize NADH and other reduced coenzymes, it is clearly highlighted the typical auscoltatory-percussion syndrome of CAEMH, shown in Fig. 1.

B) As we saw in the previous section, similarly, in young and healthy subject, pleased to do not breathe (apnea test) for $\geq$ 10 sec., semiotic-biophysics phenomenology of CAEMH is caused after a variable Lt (latency time) from individual to individual, from tissue to tissue and from side to side in the same tissue, probably in relation to evolutionary processes that in the course of phylogenesis have affected the mitochondria of different biological structures, differently in terms of quality and/or quantity without

excluding, of course, the "precise" location of mitochondrial damage genetically transmitted.

In the test of apnea, worsening shortage of O_2 causes gradual slowdown in oxidative phosphorylation, a result of impairment of electron flow along the respiratory chain and causes, in turn, histangic local acidosis, the clinical expression of which is represented by auscultatory-percussion syndrome of CAEMH, caused, as already known, by the application of digital pressure on a large number of trigger-points.

In tissues with predominantly aerobic metabolism, to maintain life and cellular function, it needs of continuous supply of O_2, obviously compromised in apnea test, in which there is also sympathetic hypertonia. In fact, this test triggers a disease situation and through the hypertonic activation of the sympathetic and renin-angiotensin system, circulating and on tissue, as demonstrated in biophysics semeiotics, clinically for the first time, with resulting alteration in hemodynamic-hemorheology of microvascular tissue units. In fact, the reduced tissue perfusion, secondary to increased tone of resistance arterioles, which have impaired vasomotion with decreasing flow-motion, is highlighted by decongestion kidney, spleen, pancreas, etc., after 4-5 seconds of transient, short (3 sec.) congestion. These are reactive changes of local blood flow designed to preserve the physiological supply of O_2 to the noblest tissues, like the heart and brain, during the emergency. Indeed, in these tissues with high aerobic metabolism, physiologically it is implemented the microcirculatory activation type I, associated, with increased blood supply to the parenchyma (the so-called active hyperemia).

In the tests outlined above, the availability of cellular O_2 is reduced and consequently there is impaired mitochondrial oxidation of NADH and other reduced coenzyme, because O_2 is the terminal acceptor of electrons which flow along the complex structures of the five complexes forming the mitochondrial respiratory chain with two compounds associated with them, the coenzyme Q_{10} and cytochrome (Egger 1981, Gadaleta 1980, Hatefi 1985). Consequence of these events is the slowing, progressive until his arrest, transport of H^+ through the inner mitochondrial membrane, cause of worsening impairment of membrane potential, electrochemical energy source, essential for ATP production, as in the chemo-osmotic theory by Mitchell (1993). Therefore, during the two tests and, of course, in Restano maneuver - simultaneous execution of these tests, the synthesis of ATP is progressively reduced, while increase the metabolites which can not be oxidized and / or removed from the tissues, as in tourniquet test with a greater tissue damage.

The accumulation of metabolites such as NADH, H^+, CO_2, lactate, causes a rapid fall of pH and, consequently, intracellular acidosis, which is a defense mechanism against ischemia and/or 'hypoxia, which aims to decrease demand of O_2 (decrease in energy histangic expenditure, for example in the myocardium) and the reduction of the influx of Ca^{++}, following the restriction of the slow channel and total cellular up-take. Indeed, in the subject with positive CAEMH-α, who "mentally" performs simple math or "think" after only 3 seconds, transient cerebral-gastric aspecific reflex turns sharply of reduced intensity and it is the same when are stimulated both the right and left cerebral trigger-points. Under these conditions, the insufficient supply of O_2 reduces more strongly the

activity in neurons which are more active from a metabolic point of view, consequently with greater reductions in local microvascular tissue units both in blood flow and in average size and vasomotor oscillations, which are essential as ground of the brain gastric aspecific reflex.

Finally, in relation to the different evolution of mitochondria in different tissues, the appearance and / or stress of auscoltatory-percussion syndrome in CAEMH after a variable Lt (latency time) appears both in tourniquet test and in the apnea test and in the Restano maneuver: for example, the Lt (latency time) is shorter when the trigger-point is represented by the upper third of the quadriceps muscle or naturally other skeletal muscle. In other words, in mitochondrial structures phylogenetically more "recent", i.e. the fingers, lips, tongue, etc. in order to provide fast, delicate, complex, sophisticated performances, local cells must have particularly effective sources of energy, i.e., mitochondria which can synthesize in a very short time requested and required energy (ATP).

With this regard it should be noted that in oxidative phosphorylation are freed 686 Kcal. per mole of glucose metabolism, while in "anaerobic" glycolysis - Cycle of Embden-Meyerhoff – are provided only 47 calories. Therefore, the hypoxic and / or ischemic state induced by tests mentioned above, negatively and more intensely affects the mitochondria which are more active but also more vulnerable, as we reported about the apparent disappearance of the auscoltatory-percussion syndrome of right brain dominance in the apnea test. In support of these statements there is the value of Lt (latency time) reflex during the apnea test in healthy and young subjects: Lt 10-12 sec. for trigger-points of the tongue and lips; Lt 12 sec. for median or middle part and 10 seconds for buccal angles, very different from the Lt reflex III lower of the quadriceps muscle-gastric aspecific which is of 14 seconds.

Clinical evidences of the "existence" of CAEMH

Numerous clinical evidences are suggesting that the auscultatory-percussion syndrome is really related to the reduced mitochondrial respiratory activity. Indeed, in patients with heart failure, respiratory failure, embolism, thrombosis syndrome, iron-, magnesium-, Co-Q10 deficiency, percussion auscultatory signs of CAEMH become very intense. On the other hand, therapies to improve or cure disease just mentioned lead to an improvement of the percussio-auscultatory syndrome and / or to a disappearance of the phenomenology of the underlying disease, in accordance with the well known parameters of Henle-Koch.

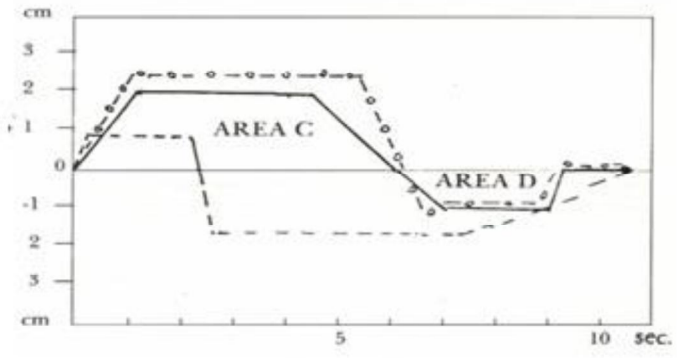
At this point, we must remember that the alteration of the mitochondrial respiratory chain provokes increasing of Ca^{++} and Na^{+} in the *smooth muscle cells*, and other cells, of microcirculatory units. Moreover, as the distribution of α-adrenoceptors in the venous and arterial vessels is notoriously different (De Vincentis 1980, Dixon 1986): during the *boxer's test* (clenching fists), i.e., sympathetic hyper tonus due to isometric work, in presence of CAEM-α, immediately appears kidney-,spleen- and pancreas-congestion of **3** cm in intensity (NN = **2** cm) and small duration, $\leq$ 3 sec. (NN = 6 sec.),

followed by a rapid decongestion, ≤ 2 sec. (NN ≥ 3 sec.), which lasts more than the normal > 5 sec. (NN = 5 sec.).

Interestingly, in the diagrams, regarding the different biological systems, doctor observes an high and prolonged phase D (Fig.2): it is sufficient, actually, to know that the persistent evaluation (for at least 1 min.) of kidney size, e.g., with the aid of auscultatory percussion permits doctor to estimate the diameters degrees, concerning intensity and periods; if these values are reported in a Cartesian axis system – even mentally – one can observe an interesting diagram, as that illustrated in Figure 2.

In the diagrams for biological systems, therefore, there is a phase C high, intense, but short-lived, as in sympathetic overtone, quickly followed by an intense and prolonged during D (Fig. 2). These clinical findings underscore a fact of primary importance for the semiotics biophysics and clinical microangiology, which is the close relation between metabolism, mitochondrial activity and vasomotion. Following these interesting correlations, it was possible to bring molecular-biological events at the clinical level with the help of the original physical symptomatology.

Renogram – rhythmic oscillations of renal volume



Legend: _____ normal subjects and after therapy
- - - - - sympathetic hypertonia and before therapy
-°-°-°-° vagal hypertonia

Figure 2. Geometrically Illustrated Clinical Observations: modifications in nephrogram of healthy in different conditions of autonomous nervous system (ANS). In CAEMH-α these fluctuations result more intense, with altered periods, as described in the text. Moreover, it is of interest that CAEMH-α represents also the conditio sine qua non of ANS tone dysfunction.

As demonstration of the validity of what above referred, there is our research data in patients with iron-deficiency syndrome, mild to moderate, with little or no clinical symptoms, which dominated the neuromuscular fatigue-muscle. The basic reflex III quadriceps middle muscle - gastric aspecific showed a high intensity, 4-5 cm. In all patients was administered a preparation of iron x os, which reduced the intensity of the reflection, down from 4, 5 ± 0.5 cm to ± 0.5 to 1.5 cm.

In conclusion, CAEMH-α is the clinical expression of congenital abnormalities of molecular-biological nature, generally inherited through the mother, which affect the mitochondrial respiratory activity with a severity that varies in a given individual, from

tissue to tissue and from side to side of the same body. This is simply implicit in the large body of empirical and theoretical data provided during 50 years of research and thousands of patients seen. The CAEMH-α, by means of lipid-glucose metabolism and through alterations and modifications of vasomotion, at level of microvascular tissue unit, especially with impaired microcirculatory functional reserve, facilitates the onset of pre-metabolic syndrome, pre-morbid state or gray instead of prevention, which can result in serious human diseases, even in the presence of acquired and environmental risk factors if not early recognized and accordingly treated.

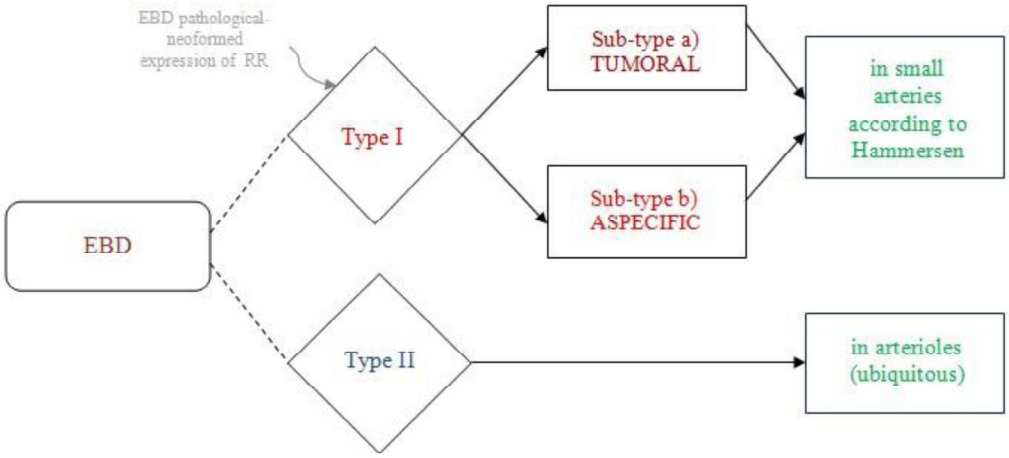
2. **Alteration of mit-DNA and oncogenesis**

To explain clearly and concisely the link between the mit-DNA and oncogenesis is useful to consider the theory of autopoiesis, well known in biology, and already introduced in this article. An autopoietic system as defined by Maturana and Varela is based on the concepts of autopoietic pattern of organization and structure. Frijof Capra suggests to complete this theory by introducing a third element: the process of materialization (or better structuration) from organization to structure. This one completes the triad organization, structure, process, and in accordance with the views of Paolo Manzelli we can use the concept of Energy Information (EI) as a principle that governs the process.

Through the objective semeiotic biophysics examination in a few minutes, it is possible to recognize and quantify if a patient has got any congenital Real Risk (RR) to have a disease by means of the observation of EBD (Endoarterial Blocking Devices within small arteries, by Hammersen), type I, subtype a) cancerogenous b) nonspecific (present in all the other more frequent and severe disease).

The EBD is a kind of dam which opening or closing itself regulates blood flow in microvessels directed to the parenchyma (tissue, substance of a body). With a simple stethoscope it is detectable if there is a clear genetic predisposition to have a disease such as cancer or diabetes, and we can quantify and monitor it over time from birth. So there is the possibility of implementing a prevention on a huge scale in individuals clinically finally selected in a rational way. This new way to prevent illness will not allow to materialize the disease, but it can be anyway potentially present (or be RR as "residual") at potential level. As similarity we can think of butterfly valves that regulate the flow and mixture of air and gasoline in car engines, since the EBD are dams that are simply regulating blood flow to the parenchyma[26], precisely cells of various tissues. If these EBD are tough, rigid, inelastic, there is RR.

There are EBDs Type I, located in small arteries (Hammersen, 1968) and Type II located in the arterioles but only type II is ubiquitous (in the sense that it is observed everywhere, in all arteries). Even these physiological types get sick or old. However, the other types, pathological-neoformed, are expressions of the RR, of potential disease, they occlude more, but through therapy they can be transformed from the subtype a)tumoral, to subtype b) aspecific, and then in "physiological" type, decreasing gradually their amount[27].



Scheme 2. Endoarterial Blocking Devices (EBD)

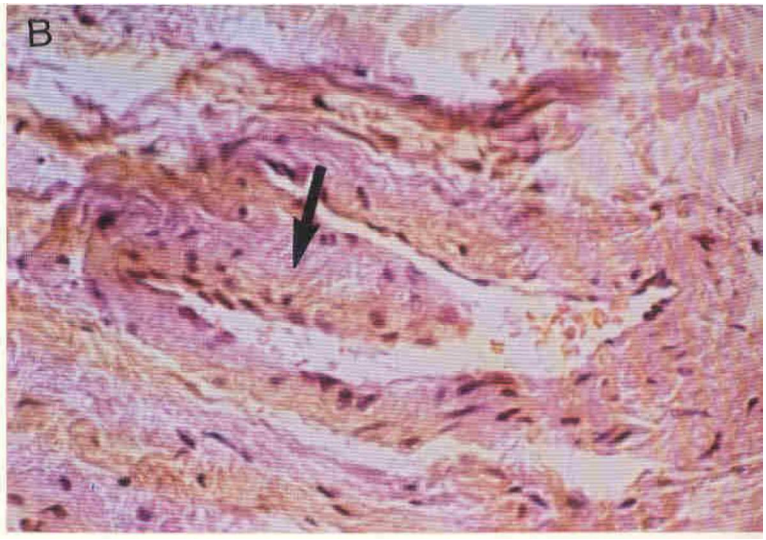


Figure 3. Endoarteriolar Blocking Device (EBD), peduncolate, proboscis-like and protruding into arterial lumen (arrow), observed in leg skin. For kind permission of Curri S.B. (1986)

The Oncologcal Terrain (OT) is instead expression of reduced defense (of gravity in growing) of the body mediated by PNEI system (psycho-neuro-endocrine-immunological system) in front of cell degeneration, and thus of the possible oncogenesis, which occurs in every individual independently of the presence or absence of OT and of the gravity of the possible CAEMH. The OT is detectable at birth, because the intense CAEMH[28] affected neuronal centers of PNEI system. Following angiobiopathy[29], then, this causes microcirculatory remodeling, first expression of tumor event, called oncological RR, when the two mutations of DNA (nuclear and mitochondrial) last long enough during which the cell physiologically heals 'crazy' or repairs the damage of DNA, or die.

Real Risk (RR) means any mutation, limited at level of cells belonging to a well-defined biological system - for example, beta cells of islets of Langerhans, for diabetes - which occurs in one or more cells when energy information EI (and EV - ATP) decreases strongly for any reason. If there is the OT, in healthy, degeneration of one or more cells

that occurs in every moment of life (intra-uterine) is repaired immediately, usually before the onset of microcirculatory remodeling: either the cell returns to social or die! Therefore, the first phase of the RR in healthy is physiological and instantaneous in the sense of immediate repair before it can occur microcirculatory remodeling, which in any case it takes very short time. It would be interesting to see, for example, the liver of a person healthy or not, for 24 hours, in search of O_2 and tissue remodeling.

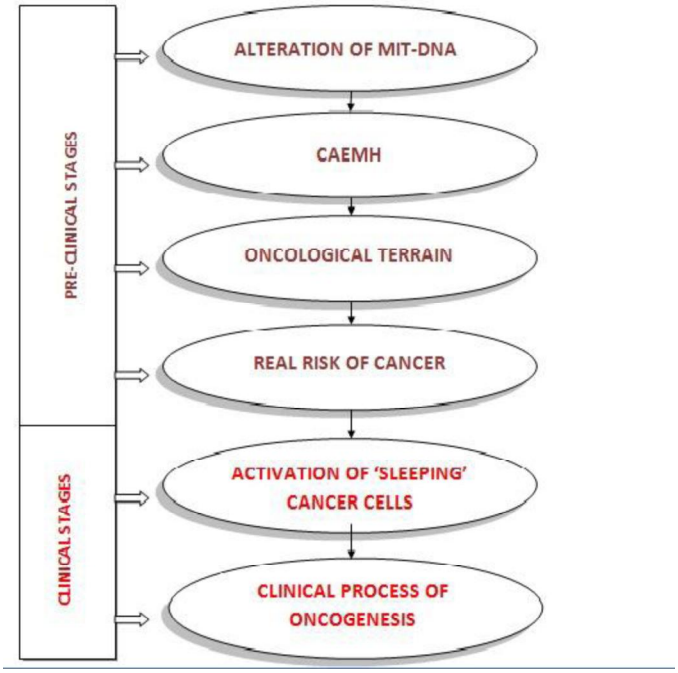
The Oncological RR in the individual with OT, when it is present at birth, is explained by the simple fact that in nine months of intrauterine life, because of parenchymal cell mutation, and angiobiopathy, the disease process was not interrupted for compromised defense system PNEI (or OT). For those who do not have OT at birth (detectable through the "reflex-diagnostic auscultatory-percussion" with the simple use of the stethoscope just in one minute) is not required prevention – he/she will never get that cancers - but for those who show OT or latent OT it needs prevention, even in the absence of RR, as might arise RR in the future due to the fact that it could diminish their level of EI for some reason (e.g. environmental risk factors as smoking and drugs).

For those who do not have any OT, it does not need absolutely any prevention: the CAEMH is present elsewhere, but not in the cells of PNEI system, because there is not OT since birth. Although it was emphasized elsewhere in isolated parenchymal cells, with possible beginning - under environmental influences – of degeneration, the process would remain under the control of the vital physiological defense organ.

We can not categorically exclude that an individual with OT but without RR at birth may never get cancer: the RR can occur at any time at all. If it does not appear and are not worsening environmental conditions, defenses, although compromised, are able to defend the body from cancer. If, for example, an individual was constant smoker, and had OT but not lung RR, he could never get sick of lung cancer until it would arise, firstly mutations in lung cells, and then, according to angiobiopathy, microcirculatory remodeling, i.e., the RR of lung cancer. So, in practice, a person who smokes for years but maintaining no RR, despite all the potential environmental risk, is expected that it will not be affected by lung cancer. This smoker has a lung level sufficient to repair both nuclear and mitochondrial DNA (his CAEMH is mild-moderate). There are so many stages of transition in oncological process, linked to different levels of EI, both in the nucleus of PNEI and those of various parenchymas.

Oncological RR affects everyone, at least in the first phase represented by parenchymal genetic mutations, but in healthy it is limited just to degeneration of only one or few cells that do not have time to cause microcirculatory remodeling: either the cells are repaired and return social or die. In this case the RR will never be observed or, if you observe it for a few moments, it would disappear quickly under the action of repair still occurring in the presence of a not intense OT.

In turn, the absence of OT at birth is a clear dividing line: in the subject, healthy from this point of view, never and ever one day could rise a OT, even if in the presence of some environmental factor would decrease drastically its EI or in case its CAEMH became intense. In fact, in this cases it will never fall below the critical level of EV, and then of EI. In fact, prolonged apnea test is positive for all the OT.

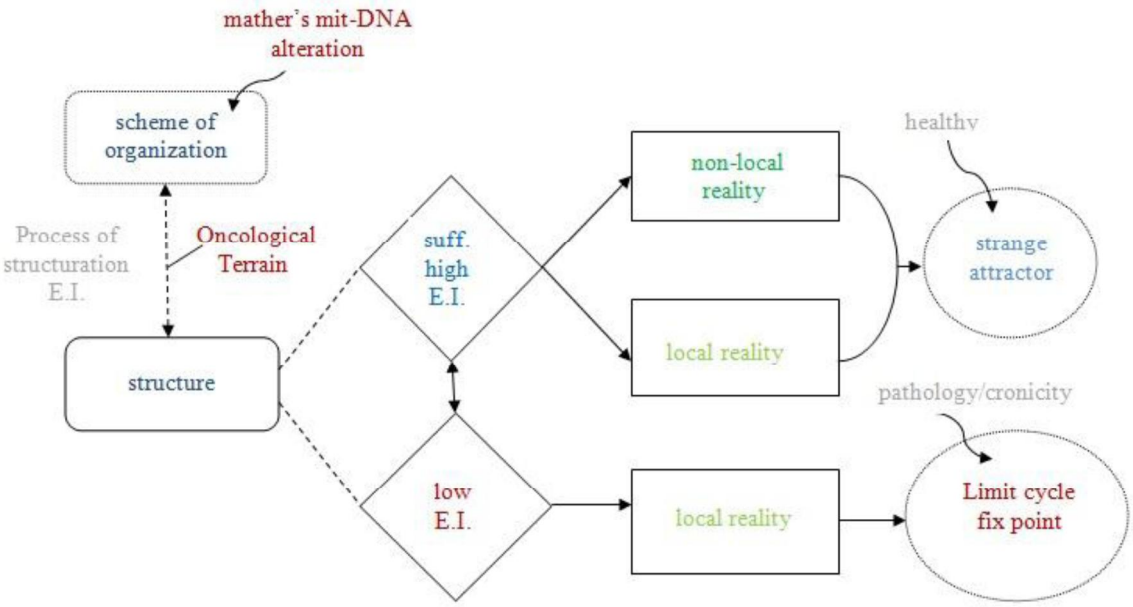


Scheme 3. The process of oncogenesis

Summarizing, through QBS the doctors are able to evaluate the pre-clinical stages of the process of oncogenesis of their patients, as shown in Scheme 3, so it is possible a pre-clinical diagnosis of the potential pathology, at bed-side, before the clinical diagnosis[30], i.e. the activation of 'sleeping' cancer cells (Stagnaro, 2004a), which start the clinical process of oncogenesis.

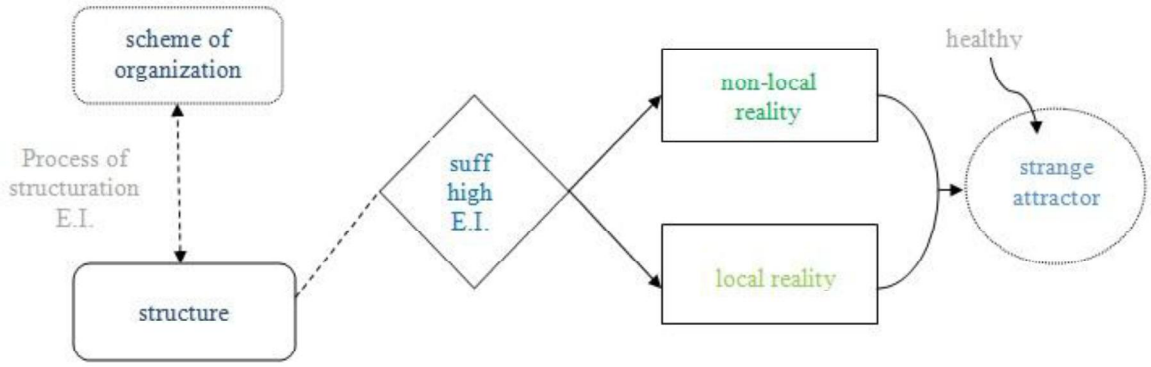
Following the autopoietic approach "scheme of organization-process-structure", similarly if there is genetic alteration of maternal mit-DNA, it is already present in the latent scheme (latent OT), but it could be that the underlying scheme is not a pattern more manifested in RR, as the level of EI would be still above a certain threshold. We must never forget the two fundamental and separated events of oncogenesis: in the center, the OT or body defenses (PNEI), and in the periphery, the parenchymal changes and the possible RR. Both are based on CAEMH. The latter, RR, arises cause the angiobiopathy, if the cell, turned a-social, lives long enough or late to become healthy under the effective control of the PNEI.

This is an essential fact in the whole discourse to understand the continuing development of the earliest stages of oncogenesis. If latent scheme of genetic alteration is manifested more (due to a level below a certain threshold of EI), then it would be obvious and measurable as RR. Scheme will materialize as structure if cancerous disease would appear.



Scheme 4. Autopoiesis and Energy Information in presence of Oncological Terrain (OT)

As shown in Scheme 4, the semiotics biophysics is able to diagnose the presence or absence of Oncological Terrain (OT) at birth, before the disease can take off, at an intermediate time between scheme and structure, allowing proper and timely preventive measures. If is detected at birth absence of OT, it is clear that no scheme could never structured in any of the cancerous diseases identified by Dr. Stagnaro. This is the boundary line.



Scheme 5. Autopoiesis and Energy Information in absence of Oncological Terrain (TO)

Scheme 5 shows that in human bodies there is physiologically the healthy co-existence of two different realities: local reality and non-local reality. The no locality disappears if the mitochondrial respiratory activity, and consequently EI, significantly decreases. For example Lory's experiment (Stagnaro 2008) fails, if is applied a stimulation in a subject following the apnea test, with the result of an impaired mitochondrial activity. The compensation takes place because of 'nuisances' involving dissipative structural changes, but always subject to the power system's inherent conservative autopoietic organization.

Without OT, every possible mutation, with or without RR, is controlled by the PNEI system, physiologically running. The same is true despite the presence of mild, initials form of OT, but if environmental conditions do not deteriorate significantly. In this case there will be intense CAEMH, even in the presence of environmental factors that affect it, by decreasing the EI, so that it can never be the OT and RR diagnose in this subject. The situation is different if we note the emergence OT or latent OT but not RR. In this case the scheme shows genetic alteration of mit-DNA, but there is no RR because EI is high enough. If during the life CAEMH would become intense, latent OT could become OT, and even OT with RR, so the disease may arise as a result of decreasing EI below a certain threshold[31].

The congenital Real Risk biophysical-semeiotic therefore arises at an intermediate stage between the scheme of organization and the structure, a first structuration from the scheme (not observable) on which we can identify it (in case there was) using simple clinical tests at bedside, in a vision in which if there were RR, it would be able to tend to a pathology (potential disease), a pathology which, if occurred, would amount to a fully structuration of the scheme of organization (e.g., genetic alteration of mit-DNA) to disease. RR, if pathologically evolving, is the slow 'eventing' of disease events. Also considered in itself, whether static, is a manifestation of the structuring process of the organization. The process is reversible in the sense that - through melatonin-conjugated[32], administration of energy (e.g., NIR-LED, near infrared light-Led), and proper diet understood in the etymological sense, etc. the RR can become "residual", so that will not disappear nor will evolve towards the structure.

The principle of the process is the Energy-Information (EI), catalytically in nature, according to Manzelli. The level of Vibration-Energy (EV) related to energy-information (EI) from the perspective of semiotics biophysics is measured on the level of tissue oxygenation: namely the latency time of reflex, which is not a reflex in true. Indeed, stimulating the trigger-points to a biological system, such as the liver, "simultaneously" there is built up a sympathetic hyper-tonicity after a latency dependent on the intensity of the stimulus-related to the intensity of liberation in the biological system of adrenaline and nor-adrenaline, we observe the nonspecific gastric reflection, stomach swells, "simultaneously" to reach the critical level of low energy or low oxygen.

Under these conditions, in fact the biological system has become thermodynamically isolated. We are in this case, in the non-local reality: there is simultaneity and synchronicity. On a completely healthy human being (without RR) EI is in fact high enough, and then there is simultaneity of information. Local and non-local reality co-exist, exist simultaneously but in parallel, they do not overlap. When EI decreases, EM –Energy Matter – as a consequence increases, and whether EI falls below a certain threshold, non-local reality "disappears" and we can observe just local reality. In summary, if there is enough high EI, there is not RR, while if there is low EI, non-transitory and not occasional - low EI in transient form, for instance, is with the apnea test in individuals completely healthy without RR – since permanent, then there is RR (associated, e.g., with Oncological Terrain).

The production of EI may be endogenous - it is created endogenously in humans through a transformation of breath in subtle and vital energy, and through mitochondrial activity - or exogenous - through the release of substances like melatonin, the adoption of an appropriate diet, NIR-LED (near infrared light) – that stimulates the mitochondrial respiratory function[33], i.e. oxidative phosphorylation.

The endogenous EI born and is formed in the mitochondria, the power plant of human body. The autopoietic system self-produces EI, by transforming EM, including food, water and O_2 - which is converted into EV-EI. Endogenously we produce ourselves the EV-EI indirectly with the breath, in the sense that vital energy is a subtle energy that occurs through breathing (it is not air, it is not breath, but it travels and is created together with it).

Exogenously the EI is created by chemical transformations and biological properties of certain food we eat or through the release of specific substances (e.g., melatonin conjugated) or certain stimuli (e.g., NIR-LEDs) to improve the mitochondrial respiration.

In biological systems the Energy-Information can be transmitted chemically - through metabolic processes - and/or electrically - with the neurotransmitters - peptides. The peptides can be imagined as "antenna", which carry information (waves) non-locally, simultaneously and synchronously by resonance (in case of non-local reality with high EI), or locally in space-time.

In biological systems the EI is transmitted through the classic routes in the local reality, using substrates that reach the target tissue via blood, lymphatic, venous (hormones, cytokines, etc.) or through the nerve pathways (neurotransmitters) characterized by polarization - depolarization: there is time and energy consumption (if I move a substance from A to B, there is energy and time). On the contrary, in non-local reality pure and catalytic EI acts according to what is known in the microscopic world, expression of entanglement, observable with the semiotics biophysics, of both worlds. DNA, like an antenna, simultaneously to "intense" stimulation on certain trigger - points, begins to "vibrate" catalyzing the reactions without energy expenditure, between the compound A and B, with production of C. For example: abdominal lateral pinch of fat "simultaneously" active function of liver PPAR (the mill that burns fat and glucose) revealed by the "simultaneous" local microcirculatory activation[34].

There is a continuous structural coupling bodies-environment in all directions. If there is a tendency to disease (RR), the complex dynamics in biological system decreases: there is no chaos or lesser according to the fractal dimension (fD), detectable through the reflex-diagnostic-percussio-auscultatory, with the simple use of the stethoscope, measuring the latency and duration of reflex. The absence of the strange attractor or of deterministic chaos, is signal of low EI, the entropy is tending to zero, then in this case there is a local reality of information transmission, there is not the non-local reality. We must therefore enter EI (or create the conditions to increase it) in order to restore a sufficiently high level of EI.

In accordance to angiobiopathy, improving mitochondrial activity in the parenchyma and in microvessel cells is involved favorably intracellular free energy and are improved various biological activities: the microcirculation will be normalized.

Semeiotics Biophysics allows accurate and direct study of being and functioning of microvessels and only indirectly of the related parenchyma[35]. If it improves the way of being and functioning of the microcirculation does mean that it also improved the way of being and functioning of its parenchyma. This is done by stimulating the activity of mitochondria by acting on the vehicles that transmit EI: metabolism (chemical process), peptides' net (electric-electronic process), but also improving, normalizing tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy is the *sine qua non* of more frequent and severe human disease and not.

Exogenous prevention and therapy (with environmental action) is done directly on EI (and related EV) at chemical level: proper diet, conjugated melatonin, NIR-LED, or at electric level: such as acupuncture, which also acts on neurotransmitters or peptides. Endogenous prevention and therapy (autopoietic) can be implemented for example through: improving the quality of breath, improvement of lifestyles and rhythm styles and slow pace of the same (e.g., eating serene, calmly, as appropriate as possible) choice of appropriate physical activities (exercise, sports), yoga, meditation, prayer.

We are composed of a continuum of biological systems that interpenetrate and interact each other, which in health conditions show a chaotic behavior (measured by the fractal dimension).

Fractal Dimension fD	**Equilibria**	**State of health**
$fD = 1$	fix point	chronicity – chronic and acute pathology
$1 < fD < 1.9$	limit cycle tending to fix point	pathology – tendency to chronicity State of variable severity of disease evolution
$1.9 \leq fD < 3$	limit cycle	initial implementation of the tendency to disease /potential pathology- i.e. Oncological Terrain (TO) – initial evolution to disease
$3 \leq fD < 3.81$	limit cycle tending to strange attractor	tendency to physiologic condition (only potential phase)
$fD \geq 3.81$	strange or chaotic attractor	Physiologic condition – healthy state

Legend: the fractal dimension (fD) is calculated as simply as the time of the disappearance of gastric aspecific reflex, before the appearance of the next. Important is that the fD is directly related to (d) or inversely (INV) related with:

A) (d) the local microcirculatory functional reserve - (vasomotility and vasomotion) and then

B) (d) with the presence, or not, of the local congenital Real Risk;

C) (d) with the latency time of gastric aspecific reflex and then with tissue pH;

D) (INV) with the duration of the gastric aspecific reflex

Chaos appears to be one of the sources of life. If chaos is not (or is missing) we can create the conditions that it emerges again. Chaos in biology is related to life: whether is missing and at the same time we can not restore it, is the end. For example, through the use of melatonin conjugated, the energy level raises and then EV-EI increase fostering and perpetuating the non-local reality parallel to local reality. If there were only local reality (which denotes a tendency to disease or pathology or potential disease) it would then need to return to a more complex order (chaotic attractor), but only if there is deterministic chaos arising from well-functioning mitochondria.

3. Conclusions

This article highlights the central role of mit-DNA in the process of tumor cell. Mitochondrial function in oncogenesis explains why cancer is a growing epidemic. Without enough energy, Energy Information (EI) associated with Vibration Energy (EV) originated by Energy Matter (EM) (i.e. glucose, amino acids, fats, etc.), the cell can not perform its normal functions. Under these conditions, therefore, the diseases arise under the action of the many negative environmental and acquired risk factors, which are not, however, to define the causes of diseases such as diabetes and cancer, since merely facilitators only for those at risk! In absence of congenital Real Risk, based on mitochondrial cytopathy, all factors achieved are innocent bystanders (Stagnaro, 2009b).

In conclusion, the doctors are now in a position to evaluate with a simple stethoscope the way of being and functioning of mitochondria, in any biological system of their patients, so that they can provide appropriate, targeted and effective prevention and treatments.

As point of reference for medicine and further researches in this field there is the fact that we have to consider the slow patho-physiological pathway from health condition to disease: from the healthy stage, white zone, very slowly, one reaches the disease onset, black zone (i.e., dyslipidaemia, gout, malignancies, etc.) going through the pre-morbid stage, grew zone, that can last years or decades, without clinical symptomatology.

Since we do not know, at the moment, neither all gene mutations nor the precise beginning of the first vascular abnormalities (as well as those of related parenchyma), it appears to be an important and essential event the use of a “clinical” tool, reliable in detecting the presence as well as the severity of such microvascular structural abnormalities (i.e., EBD abnormalities), as a convergence of the effects of gene mutations, interacting with environmental risk factors.

When Henry Poincaré observed the footprints of chaos in early 1900 was deeply impressed by its complexity and beauty. Finally discovered by Edward Lorenz, meteorologist of Massachusetts in the 60s, he could not realize the extraordinary scope of his revolutionary discovery, which became evident only in subsequent decades. 47 years have elapsed since then, and that his article "Deterministic non-periodic flow" (Lorenz, 1963) became the cornerstone and the initial condition of unforeseen and unexpected consequences, particularly in science: the butterfly effect for excellence.

Today, the deterministic chaos emerges everywhere: in quantum physics, chemistry, biology, genetics, neuroscience, cognitive psychology, economics, art, cryptography, meteorology, even in the stock exchange.

This article celebrates the importance of complexity theory in medicine, following a multidisciplinary approach where biology and quantum physics, chemistry and modern genetics, are walking softly in harmony, penetrating each other, on its wake and assistance.

Furthermore, chaotic determinism, and quantum determinism as suggested by David Bohm, could merge together in a new philosophical idea of 'quantum-chaotic determinism'[36], corroborated by QBS and Manuel's Story[37], where the 'cause and effect' is replaced just by a potential causality.

"In the human body and animal there is deterministic chaos that is not disorder, but a higher order type in physiology. Only in the pathology there is a lower order: the measure of the first order is an equilibria called strange attractor, while the measure of the second one is called fixed point.

In case of fixed point equilibria the biological systems are linear, but when sufficient energy is introduced in them and they are properly stimulated, they show the characteristic behavior of non-linear dynamical systems far from equilibrium (dissipative). Chaos requires enough energy to activate dissipative mechanisms, and life is the trajectory of an attractor: from strange attractor to fixed point, passing through the limit cycle.

The main task of the doctor is to recognize promptly the various moments of the trajectory of the patient's life (in all and each of its biological systems), to intervene rapidly with appropriate therapy, useful and effective to reverse the dangerous direction of the trajectory toward irreversibility."

An example of this with incontrovertible evidence of the presence of deterministic chaos in the human body is given by clinical microangiology[38] where the universal constant of Feigenbaum (mark of chaos, comparable in importance to the greek *pi* - π, the golden section *phi*, and the number *e* of Euler) always emerges as a relationship between the fractal dimension (fD) [39] and the latency time (for example, gastric aspecific reflex) in healthy subjects, while in the disease this measure disappears.

This article is a hymn to life. The chaos as the life is inherently unpredictable, full of beauty, harmony and charm. The deterministic chaos is signal of life! If all this were to fail, as when the sublime energy of love tends to fade, you would inevitably encounter different equlibria of lower order, pathologies, diseases, chronic or heat death, in biology.

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Endnote

[1] NHS stands for National Health Service

[2] Mendel (1822-1884), studying the behavior of chromosomes in the nucleus, showed that the hereditary characters are transmitted as a unit. Chromosomes are located in individual hereditary characteristics of these units, and then called genes. The transmission of characteristics from parents to offspring is called heredity: the majority of such characters of an organism pass from parents to children when organisms reproduce. But he had no knowledge of the existence of mitochondria described by Altmann in 1894 and rediscovered by Benda in 1897, who baptized them with their current name.

[3] The human mitochondrial DNA is inherited by matrilineal (not Mendelian inheritance) as during the process of fertilization of sperm mitochondria are marked with ubiquitin, a protein that binds to other proteins to be degraded. As a result, the mitochondrial genome of the offspring will be almost equal to the mother (subject to possible mutations) and also if the mother is suffering from a mitochondrial disease transmission, then all children inherit. In literature there are very few reported cases in which the mitochondrial DNA seems to derive from the father or both parents.

[4] Lyapunov Characteristic Exponents – LCE – is a statistic measure to test the presence of 'sensitive dependence on initial conditions' – SDIC – in a system. SDIC is at the root of the 'disorderly' behavior of deterministic dynamical systems and is responsible for their random appearance and unpredictability.

[5] Fractal dimension is a measure of the way orbits fill the phase space under the action of a flow or a map, suitable for fractal objects, characterized by a non-integer dimension.

[6] Entropy is a measure of the uncertainty in deterministic dynamical systems, or equivalently is the amount of information we get on the average by making an observation. In particular, the presence of positive entropy indicates that the observation of the system continues to generate information for an arbitrary long interval of time. Consequently, unless the position of the system can be observed with absolute precision, there will forever remain uncertainty about its future course, even when the dynamical rule governing the system is known with precision. Zero entropy is interpreted as absence of chaotic or complex behavior, typical of linear or periodic systems with fixed point or limit cycle equilibrium, so that they are fully and exactly predictable: none new quality information emerges for an arbitrary long interval of time.

[7] The particle paths fluctuate chaotically, so that causal interpretation is not strictly deterministic as in Newton physics: unpredictability and uncertainty are intrinsic property of the deterministic dynamical systems observed, as in chaos theory, and not random or casual like in classical interpretation of N. Bohr.

[8] This electron turns out not to be a simple structureless particle but a highly complex entity that is effected by the quantum potential – QP - in an extremely subtle way. Indeed QP is responsible for some novel and highly striking features which imply qualitative new properties of matter that are not contained within the conventional quantum theory.

[9] Unlike the particles of Newtonian physics, the electron is never separated from a certain quantum field which fundamentally affects it, and exhibits certain novel features. This quantum field satisfies Schrödinger's equation, it is therefore causally determined.

[10] The form of QP can dominate behavior: information contained within QP will determine the outcome of a quantum process. There is an active information, a form having very little energy enters into and directs a much greater energy. There is an energy form acting to inform.

[11] Information, from the latinum verb 'in-formare', which means 'to give a form' is a truly more primitive fundamental activity than energy and matter, is something that precedes every physical form (Aristotele). Information's action is therefore related to the potential codification plan of producing an objective form and in turn we can perceive an object as form's of information transmission.

[12] (1) $EV + EM + EI = k$ the sum of the three energy is constant

(2) $\Delta(EV + EM + EI) = 0$ differentiating (1) the sum is zero

(3) $+\Delta EI = - \Delta EV - \Delta EM$ these equation evidences the relationships between these 3 energies

[13] The implicate order is fundamental while the explicate order is understood as having unfolded from the implicate order. The particles of physics are like dynamic structures which are always grounded in the whole from which they unfold and into which they enfold. There may be a further unknown set of entities, each having its implicate order which goes deeper and deeper without limit and is ultimately unknown and indescribable totality is called holomovement, which acts as the fundamental ground of all matter.

[14] See note 12. For example, the decrease of ATP (EV), generates an increase of lactic acid (EM)

[15] The meaning of entropy in chaos theory (note 6) has not to be confused with entropy in thermodynamics, as in chaotic equilibria there is not dis-order, since higher complex orders, according with the view of David Bohm, so that if the rate of entropy is more than 0 and growing up, it does mean that there is deterministic chaos, while entropy less than 0 means periodic of fix point equilibria (absence of qualitity informations step by step given by the observed dynamical system). http://www.scienzaeconoscenza.it/articolo/entropia.php

[16] See http://www.semeioticabiofisica.it english version

[17] Paper in progress

[18] See http://www.latimes.com/features/health/la-he-practical-matters-20100412,0,2670974.story

[19] Oxidative phosphorylation is a metabolic pathway that uses energy released by the oxidation of nutrients to produce adenosine triphosphate (ATP). This is the final stage of cellular respiration, after glycolysis and Krebs cycle. During oxidative phosphorylation, electrons are transferred from electron donors to electron acceptors such as oxygen, in redox reactions. These redox reactions release energy,

which is used to form ATP. In eukaryotes, these redox reactions are carried out by a series of protein complexes within mitochondria, whereas, in prokaryotes, these proteins are located in the cells' inner membranes. These linked sets of proteins are called electron transport chains. In eukaryotes, five main protein complexes are involved, whereas in prokaryotes many different enzymes are present, using a variety of electron donors and acceptors.The energy released by electrons flowing through this electron transport chain is used to transport protons across the inner mitochondrial membrane, in a process called *chemiosmosis*. This generates potential energy in the form of a pH gradient and an electrical potential across this membrane. This store of energy is tapped by allowing protons to flow back across the membrane and down this gradient, through a large enzyme called ATP synthase. This enzyme uses this energy to generate ATP from adenosine diphosphate (ADP), in a phosphorylation reaction. This reaction is driven by the proton flow, which forces the rotation of a part of the enzyme; the ATP synthase is a rotary mechanical motor.

[20] See *Clinical Microangiology* – Dr. Sergio Stagnaro – http://www.semeioticabiofisica.it/microangiologia/common_eng.htm

[21] See http://www.semeioticabiofisica.it – english version

[22] See http://www.semeioticabiofisica.it/semeioticabiofisica/oncological.htm

[23] See glossary in http://www.semeioticabiofisica.it and http://www.semeioticabiofisica.it/semeioticabiofisica/Oncogenesis.htm

[24] The terms "light", "medium" "intense", have a precise and quantitative scientific value, understandable only if it is known in depth the microangiological semeiotic biophysics, as they are related to the effect on different structures resulted in the microcirculation, from time to time, depending on the intensity of stimulation.

[25] See the glossary in http://www.semeioticabiofisica.it

[26] The parenchyma is a characteristic substance of the bodies such as the liver and the lung parenchyma.

[27] See Microangiology in http://www.semeioticabiofisica.it

[28] There are n – DNA alteration, for example, in Oncological Terrain. However, if we correct the functional mitochondrial error (CAEMH) with melatonin, NIR-LED and regular life, diseases do not usually occur. Then, the onset of diseases such as diabetes, cancer, hypertension, is observed when – in presence of n-DNA alteration – the EV decreases (tissue acidosis), but is possible to correct by increase of EV (mitochondria that work well) and consequently increasing the EI (restoring the non-local reality) and disease does not arise at least in most cases. Alteration of the genome requires the reduced EI!

[29] See http:// www.semeioticabiofisica.it

[30] Metabolic syndrome is a combination of medical disorders that increase the risk of developing diseases. The pre-metabolic syndrome, as defined by Stagnaro, is the syndrome that precedes the metabolic one, and is linked with congenital real risks and their associated biophysical semiotics constitutions.

[31] What is the difference between residual RR and TO without RR in terms of EI and fractal dimension (fD)? The quantization of TO is perfectly realized on the basis of the parametric values of the reflection SST-RH - gastric aspecific reflex: latency time (Lt) in seconds and duration of reflection in seconds: NN Lt = 8 sec., duration 3 sec. to less than 4 seconds (Microcirculatory Functional Reserve RFM, an expression of the way of being and function of local microcirculation and of fD), if the stimulation is of medium intensity.

A) light but existing TO (not latent): Lt still NN - 8 sec. - but duration of reflection exactly 4 sec. (NN < 4 sec.)

B) mild-moderate TO Lt 8 sec and duration 4, 5 sec.

C) moderate TO Lt 7,5 and duration 5 sec.

As shown in the experimental evidence with the apnea test grades are correlated with the mitochondrial respiratory activity!

[32] Melatonin is a natural substance that our body produces itself. It is produced by synthesis in the laboratory and placed in the body is to act on mitochondria, especially increases mitochondrial

phosphorylation, it produces more EV and therefore greater EI and this must be for the benefit of the entire body, improves breathing (especially at night; we produce melatonin mainly from the early hours of the night until around dawn), and therefore this is a hormone that is universal and is good for the treatment of multiple diseases, or tendencies to pathology, and then to make the RR residual. It is also a good neurotransmitter.

[33] In therapy, based on what has been observed in patients with Oncological Terrain places on the nodes of Curry or Hartmann (worsening of PNEI - psycho-neuro-endocrine-immune system), these energies released will improve and normalize respectively, by their influence on the alignment device, the orbital motion of subatomic particles, including the mitochondrial respiratory chain, which first reacts.

[34] Lory's experiment is based on the fact that "all" subatomic components and then atomic and molecular structured to form a cell and the whole cell or parenchyma, are correlated between themselves and with "all" the other branch of the same embryological in a four-dimensional space, like they are just "plot" (entanglement) two electrons observed by Aspect in his famous experiment. The effect of' entanglement means that the information takes on a "non-local" dimension. Lory's experiment is as follows: if it is done a digital pressure applied over a parotid gland, or a salivary gland sublingual, of a "single ovular" twin sister, simultaneously it is observed microcirculatory activation type I associated in the pancreas of the other twin sister, regardless of the distance that separates them: meters or kilometers (see in the references Manzelli and Stagnaro).

[35] The micro-circulatory remodeling is directed by the way of living and working on the parenchyma: if the subject is healthy, is healthy the related parenchyma on the microcirculation (see angiobiopathy theory, dealing with diseases of blood and lymph vessels in accordance with the semiotics biophysics). Certainly a loss, rheumatism, immune, infectious, can act both directly and indirectly.
See [http://www.semeioticabiofisica.it/microangiologia/common.htm]. It may be that in the long run re-organization becomes difficult or impossible because the flow decreases more, and then are built up of feedback mechanisms for which are to activate dormant cancer cells. Aging with free radicals that accumulate contributes to further damage both micro vascular and parenchymal: even endothelium (cell layers lining the inner surface of blood vessels and heart chambers) and smooth muscle cells possess mitochondria. Remodeling micro circulatory type cancer is an expression of mutations of genes within cells in that forum: any change in gene expression - cell finds its expression in the parallel alteration of its microcirculation (microvascular tissue units): the tissue here is around the vessels, interstitial, not the parenchyma! If these processes are blocked, stops the entire organization. Very important is that if there are congenital abnormalities, genetically transmitted through the mother (see CAEMH, mitochondrial cytopathy or mitochondrial functional pathology in the site www.semeioticabiofisica.it) amending the unfolding vital physiological processes occur the most serious human diseases, and not, now real epidemics. Autopoietic networks must therefore regenerate themselves continuously in normal and physiological way, to maintain its organization.

[36] See the article about quantum-chaotic determinism in http://www.scienzaeconoscenza.it/articolo/la-semeiotica-biofisica-quantistica.php

[37] Manuel is born on February 28th, 2010, and he is negative for OT (Oncological Terrain) even if both mother and father are positive for OT, but they accepted to be under QBS treatment with Conjugate Melatonin by Di Bella-Ferrari, before having children, so that their Real Risk of Cancer became residual, and furthermore their son, Manuel, is living and will live without any risk of cancer forever. Stagnaro et al. (2004b) argued the chance to act directly on the mit-DNA in order to defeat cancer, and their theory and forecast became reality for the first time last April 2010. This fact demonstrates that the scheme of organization (alteration of mit-DNA) is reversible, giving real hope that cancer can be completely eradicated. Furthermore, in this sense causality is just potential, an ex-post interpretation, and it is legitimate the free will. Quantum-chaotic determinism is based on SDIC (sensitive dependence of initial conditions), quantum no locality and discontinuity, and free will, where this is possible.

[38] See "Microangiologia clinica e numero di Feigenbaum"

http://ilfattorec.altervista.org/fcappendice.html

[39] Fractal dimension (fD) calculated in the most simple way, practical, but reliable, is the measure in seconds of the duration of the disappearance of nonspecific gastric reflection before the onset of the next. This value corresponds to the effectiveness of local microcirculatory functional reserve (RFM).