Unmasking the secrets of cancer: water type A non-structured promotes carcinogenesis and water type B structured restores the physiology and cellular bioenergetics transforming cancerous cells into normal cells. Hypothesis of carcinogenesis

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"The love and the study are the needle and the line that weave the Medicine"
JFJ
"The knowledge and the dedication are the father and mother of Medicine"
JFJ
"We dream with the day that the Temple of Knowledge which teach medicine will not graduate just simple repeaters of information, but real medical doctors who learned the fundamentals of free thinking"
JFJ
"The doctor is the responsible for the patient, to gag him and to restraint him it is crime that hurts the own patient's rights"
JFJ
"Nobody can stop the actions of the real doctors"
JFJ
"The true cause of the diseases and the MEDICINE not yet made the mend fences. It is because the MEDICINE is still very young. And what about the treatments"
JFJ
"The diseases are very old and nothing about them has changed. We are the people who changed when we learn to recognize in them what before we didn't realize".
Charcot

Hypothesis of Carcinogenesis: The persistent chronic inflammation/irritation causes in the cells at inflammatory site a slow decrease of cytoplasmatic kosmotropos osmolytes which slowly causes the change of water B structured into water A non-structured which gradually reduces the degree of order-information of the thermodynamic system of the cell that when reaching the bearable maximum point of entropy causes in the cell a "state of almost death". At this point of low concentration of osmolytes, prevalence of water non-structured and high cellular entropy, the cells transform and fight to stay alive and the only way to survive is through cell proliferation. They put in place millenary mechanisms of survival, precisely those who have maintained the normal cells in the Planet during Evolution. Thus, it occurs activation of factors and ways of signaling, cytoplasmatic alkalization, prevalence of the Embden-Meyerhof cycle, etc., which promote the neoplasic cellular proliferation, the decrease in apoptosis, the formation of new blood vessels and the impediment of the cellular differentiation. The prevalence of the intracellular water type A increases the cellular hydration and cell volume. The strategies that turn the water type A non- structured into the water type B structured restores the physiology and cellular bioenergetics and neoplasic cells are differentiated in normal cells and go to the physiological process of continuous programmed cell death.

When normal cells are submitted to a regime of persistent or chronic stress (chronic inflammation, chronic infection, chronic irritation, chronic poisoning, chronic hypoxia, chronic acidosis etc), they started to live in a place with inflammatory interstitial hiposmolalidade. As a defense mechanism to keep the cell volume, they have lost kosmotropos osmolytes or decrease in kosmotropos osmolytes for caotropos. With the maintenance of chronic stress that can last for years, gradually reduce the concentration of kosmotropos solutes and structured water B, progressively turn into non-structure water A. The energy metabolism also progressively comes from oxidative phosphorylation of large production of energy to anaerobic metabolism of low energy production. In a first stage we see the change of the cell's function and with the evolution of the process; we have the change in its structure. All this happening slowly and in small proportions of a silent mode and signs or symptoms can't be noticed by a proper clinical doctor or by the image exams that we have nowadays.

The gradual increase of the non-structured water reduces gradually the degree of orderinformation of the thermodynamic system of the cell until reach a point of maximum limit of entropy with serious alterations of the physiology and of the cellular bioenergetics. When reaching the maximum limit of entropy, the cell enters in a "state of almost death" discards the heavy mechanism of the mitochondrial oxidative phosphorylation and raisin of state "Beta" for state "Alpha" where the anaerobic metabolism of Embden-Meyerhof of low production of ATP prevails. It means that the cell returned to work in archaic stage of evolution where reigned the saturation electronics, the hypoxia and the excess of reducing agents. At this point, the cell put into action millenary mechanisms of survival and activates oncogenes and factors and ways of signaling, alkalinize the cytoplasm and active enzymes of anaerobic glycolysis which together cause an increase in cell proliferation, inhibition of apoptosis, the production of new vessels and the inhibition of cell differentiation: cancer.

They are not evil cells or cancerous cells there are neoplasics cells or transformed cells, trying to increase the degree of order-information, struggling to reduce the entropy, struggling to survive. They are cells whose goal is to live.

When the predominant water in the intracellular with normal physiology of the type B, of low density, osmotically inactive and rich in hydrogen bonds becomes type A water, of high density, osmotically active and poor in hydrogen bonds occurs increase in the cell hydration with increase of cellular volume.

All the factors and ways of signaling as the NF-kappaB, STAT-3, SAP / MAPK, VEGF, EGF, PDGF, etc., constituents millenary of normal cells, which are put into action in traumatisms, wounds, fractures and physiological processes of healing and control of infections are the responsible for our survival on the Planet. At the "state of almost death" these survival mechanisms are activated and all together promote the cell proliferation redemptive of dying cell. Thus, these elements are nothing more than secondary effects of neoplasic process, reactions that are part of the mechanisms of survival at any cost and therefore late signs of carcinogenesis. They are in the right extremity of the carcinogenic process. At the left extremity of the process is the decrease of the concentration of cytoplasmatic osmolytes

The support of this hypothesis was divided into 10 parts:
I-Water
II-What tells us the chemical composition of water: H2O
III-In normal cells coexist two types of water: Type A and Type B
IV-Evidence that in tissue cancer we can find the decrease of cytoplasmatic osmolytes.
V-Evidence that in cell proliferation predominates the water type A
VI- Activation of factors and pathways of cell signaling and "oncogenes" and cytoplasmatic alkalization are secondary to the "state of almost death"
VII-Other special features of the neoplasic cells:
VIIa-Increase of cell hydration
VIIb-Increase of cell volume
VIII-Life-Order-Information-Entropy
IX-The "state of almost death" changes the place of ATP production of mitochondrial oxidative phosphorylation for the cytoplasmatic anaerobic metabolism
X-Cancer treatments increasing the structured type B water in relation to non-structured type A water
Xa- Interstitial hyperosmolality derives from the cytoplasm the water type A and decreases cancer cell proliferation.
Xb- Intracellular increase of kosmotropo substances structures intracellular water and has anticarcinogenic effect.

I-Water

Water is one of the most extraordinary substances that are present in the world; it has its own personality and contradicts everything we know of classics chemistry and physics. It doesn't follow nor the principles of the Periodic Table of Elements of Dimitri Ivanovitch Mendeleev.
It is the anomalous character of water that makes it the most important substance of our body. It is the molecular structure of water the responsible for the existence of living beings and there would be no life without water, as we know nowadays (Felippe-February 2008).
One of the most creative researchers who have already gone through this world, Albert Szent-Gyorgyi, said that water is the materia, the matrix and the mother's life and that the molecular structure of water is the essence of life.
This anomalous behavior of water is due to the presence of hydrogen bonds and water-water bonds.
Hydrogen bondings are atomic bonds of hydrogen atom from a molecule of water with the oxygen atom of another water molecule forming clusters of several molecules of water or (H2O)n, where "n" is the number of molecules of water connected by hydrogen bonds.
Hydrogen bondings with high or low randomic force are required in intracellular to:
1 - Stabilize the conformation of the helices of the DNA and RNA which maintains the molecule structure and its special feature of the roll and unroll helices,
2 - Maintain the three-dimensional structure of enzymes and proteins,
3 - Stabilize the tertiary structure of enzymes and proteins,
4 - Maintain proteins, nucleic acids and macromolecules, hydratation,
5 - Stabilizes, maintains and protects the cytoplasmatic and mitochondrial membrane,
6 – Interferes in the cytoplasmatic membrane potential (Em) and in the mitochondrial membrane potential (Delta-psi mt),
7 - Interferes in homeostasis of cytoplasmic and mitochondrial membrane pores,
8 - Interfere in the speed of chemical intracellular reactions,
9 – Participate in hydrolysis reactions,
10 - Transmit information, etc. ....

Thus, the hydrogen bonds are crucial in cellular physiology because operates as a solvent, solute, stabilizing structure and vehicle of information, so that the cells can fully comply with their duties and can be considered normal.
It is important to note that clusters of water are created by the interaction of tiny quantities of organic or inorganic substances with water, the osmolytes (Lo-2000, Wiggins-1971-2001, Chaplin MF-1999) and being classic in literature the existence of osmolytes that build (kaotropos) and osmolytes that destroy (caotropos) the hydrogen bonds of intracellular water. The first ones increases amount of type B water in intracellular and the latter increases type water A. About it, we will write more later.
The human body contains 60% of water (42 liters in a man of 70 kg with normal thin mass and 12% of fat), distributed in intravascular (5% or 3.5 liters), in interstitial (15% or 10.5 liters) and the remaining 28 liters in intracellular. The cell contains 80% of water and 20% of solutes. We are a mobile aquarium and the medical doctors only think in solutes, never in water.
II-What tells us the chemical composition of water: H2O
The water is dissociated in cations H3O+ and anions OH- and it is in constant dynamic balance, in accordance with the reaction below:

$$2H_2O \rightleftharpoons (H_3O)^+ + (OH)^-$$

Cation H3O+:
1 - Reduces the cytoplasmatic pH, it acidifies the intracellular environment and prevents the cellular proliferation.
2 - It is a powerful kosmotropo agent: structures intracellular water and prevents the cellular proliferation.

Anion OH- :
1 - Increases the cytoplasmatic pH, alkalinizes the intracellular environment and facilitates intracellular cell proliferation.
2 - It is a powerful agent caotropo: makes non-structured intracellular water and facilitates intracellular proliferation.

Water is formed by 2 hydrogen atoms and 1 oxygen atom.
Hydrogen atoms are reducing (antioxidants) and therefore decrease the intracellular redox potential and acts as agent to facilitate proliferation.
Oxygen atoms are oxidants and thus increase the redox potential and act as agents that prevent the proliferation.
In this way, the water molecule is composed by elements that facilitate or prevent cell proliferation depending on they are ionized or not. And the same element may work in one way or another depending on this state.

III-In normal cells co-exists two types of water: Type A and Type B

For a long time we know that in intracellular there are two types of water. Philippa Wiggins, the New Zealand researcher who studies the water for more than 40 years, cites the studies of Henderson (1913) and Robinson (1994) with Vedamuthu and 1997 and 1999 along with Cho that culminated in fundamental discovery to understanding the exact physiology of the cell. Those authors verified that in the cytoplasm of mammals co-exist two types of water; that is the life of cells depends on two types of water (Wiggins-1971, 1972.1990 ABC, 1999, 2001).
With didactic purpose we will call them water A and water B:

Water A: high density, osmotically active and fluid to have weak hydrogen bonds.
It is a water without structure (non-structured), with small clusters; in other words, with the "n" in (H2O)n too low.
Density: 1.18 g / ml

Water B: low density, osmotically inactive and viscous to have strong hydrogen bonds.
It is a structured water, with larger clusters; that is, with the "n" in (H2O)n high and of great duration.
Density: 0.91 g / ml

IV-Evidences that we found decrease of the citoplasmatic osmolytes in the neoplasic tissue

In the evolution of the human species, during the transition of the primitive organisms of the aqueous way for the terrestrial the genes suffered mutations and parallelly they provoked the necessary decrease of the cellular proliferation with increase of the differentiation and still provided protection against drying cell, without which the organisms would not survive in no-aqueous atmosphere. The protection against desiccation was provided by the accumulation of organic and inorganic cytoplasmatic osmolytes (Ferraris-1999-2001, Dmitrieva-2006).
In carcinogenesis occurs the opposite of what happened in evolution, that is, we observed increase in cell proliferation with decrease of the differentiation and following this reasoning we can infer that the mechanism against cell desiccation also been reversed, therefore we hope to find in the cancerous cells a decrease of the organic and inorganic osmolytes.
In fact, in the medical literature of good level, we found several scientific works that show that tissue cancer has drastic decrease of osmolytes in relation to the corresponding normal tissue.
Interstitial hypertonicity actives transcription factors (TonEBP / OREBP - "tonicity-responsive enhancer / osmotic response element binding protein) that results in increase of the genes expression involved in the accumulation of osmoprotectors organic osmolytes (Burg-1995-2007, Zhou-2006). Interstitial hyperosmolality causes an increase in cytoplasmic osmolytes as a mechanism of defense to avoid drying / dehydration of the cell. This is one of the oldest mechanisms that allowed the passage of life from water to land. The primitive organisms that managed to avoid desiccation were those who managed to live outside the water.
From the opposite side, we believe that the interstitial hypotonicity promoted by persistent chronic inflammation edema, inhibits the transcription factors TonEBP / OREBP which causes a decrease of cytoplasmatics osmolytes.
Let's study now specific scientific works about that problem in humans.
Tugnoli and Tossi in 2000 examined samples of renal cell carcinoma from 10 surgical patients, through 1H MRS (1H magnetic resonance spectroscopy). They studied in-vitro, 10 tumor samples and 10 samples of normal tissue around the tumor. The MRS tells us about the osmotically active substances of renal cell (osmolytes) that are classically considered as physiological markers of kidney function.
The authors found a marked decrease in cytoplasmic osmolytes in tumor cells and considered this fact as the seal which signifies the presence of cancer.
For Felippe Jr., the decrease of the osmolytes provokes prevalence of the water type A what provokes alteration of the function in the initial phase of carcinogenesis and later in the evolution with the great increase of non-structured water and the change for anaerobic metabolism unchain the cancer.
In 2003 Tugnoli studied the biochemical composition of the normal and neoplasic renal tissue through MRS (magnetic resonance spectroscopy) and the HPLC (high performance liquid chromatography). Thirteen patients were examined with nefrocarcinoma, of which 24 samples were taken from tissue: 13 of nefrocarcinoma itself, 9 of normal parenchyma around the tumor and 2 of the cortex and medulla healthy kidney. The MRS gives us information about the intracellular osmolytes and HPCL about the amino acids composition.
In nefrocarcinomas was found GSH, reduced glutathione, supplier of hydrogen atoms that promotes cell proliferation. In non-proliferative tissue hadn't found GSH.
In the normal tissue, osmolytes were present in physiological quantity while in the cancer tissue there was marked decrease in osmolytes.
For Tugnoli a marked decrease in osmolytes is typical of cancer. However, we believe that cancer happens only when the amount of osmolytes decreases until the point that provokes non-structured cytoplasmatic water at the maximum level of entropy supported by the cell. In other levels we have only cell dysfunction without cancer.
In 2007 Tugnoli and Righi studied cancer and normal tissue kidney through HR-MAS-MRS (high-resolution magic-angle spinning magnetic resonance spectroscopy) from five patients, three with renal cell carcinoma and two with papillary renal clear cell carcinoma. All patients were underwent radical nephrectomy and fresh tissue from normal cortex, normal medulla and tumor were studied by the HR-MAS-MRS.
In normal cortex and medulla they found the presence of osmolytes showing the condition of normal tissue physiology. In clear-cell carcinoma they found marked decrease or even disappearance of osmolytes. In papillary carcinoma they found a great amount of taurine.
That researcher shows that in normal cells the osmolytes are present and therefore also present type B structured water which maintains the normal functioning of cells.
In renal clear cell carcinoma occur decrease of osmolytes and therefore increases the non-structured water type A. In papillary carcinoma they found increase of the amino acid taurine that some researchers believe is a caotropo substance, that is, it increases the amount of type A water in the cytoplasm.
Thus, we show concrete evidence that we really find decrease of osmolytes in cancer tissue.

V- Evidences that in the cell in proliferation prevails the water type A

Many evidences indicate the prevalence of high density and osmotically active non-structured water type A in proliferating cells.
Hazlewood in 1971 showed changes of water status in the development and proliferation of normal muscle and after that, Damadian suggested that undifferentiated cancer tissue could be diagnosed by the same technique: the "spin-lattice relaxation time" T1 and T2 of protons of water by Resonance Nuclear Magnetic (RNM).
The following years, appeared in the literature, works corroborating the research of Damadian. They were human tumors transplanted in animals that could be distinguished of the corresponding normal tissue by the technique of RNM: fibrosarcoma, linfosarcoma, melanoma, rabdomiosarcoma, tumor of round cells and tumor of fusiform cells(Weisman-1971, Hollis-1973).
Many works appeared in "in vitro" humans experiments indicating that Damadian was correct: breast (Eggleston-1975, Goldsmith-1978, Medina-1975), lung (Goldsmith-1977), thyroid (De Certaines-1982, Shara-1974), and brain tumors (Benoist-1981, Chatel-1986, Parrish-1973).
Hazlewood in 1972 researching the intracellular water with the technique of RNM of cytoplasmatic water protons of the mammary mouse gland got the feat of distinguishing the pre-neoplasic state of the neoplasic state.
In 1975 Hazlewood along with Medina, studying the intracellular water by RNM of the human mammary gland cells managed to show the differences between normal tissue, disease not neoplasic and neoplasic disease: gradual increase of non-structured type A water in respect of structured type B water.
These findings support the hypothesis of Felippe Jr that the gradual increase of non-structured water causes in a first stage the cellular dysfunction (disease) and at the final stage with the progression of the increase of the type A water, appear cell proliferation (cancer) that is triggered by maximum degree of functional change: "state of almost death" (Felippe-February-2008).
In 1980 Hazlewood with Beall in mouse mammary cultures cell using the same technique was able to distinguish normal cells, pre-neoplasic cells and neoplasic cells, by the characteristics of intracellular water. The values of T1 of the water protons (spin-lattice

relaxation time) for normal cells were 916 + / -24 msec; for the pre-neoplasic cells 1029 + / -24 msec. and for the neoplasic cells 1155 + / -42 msec. In the distinction between normal and neoplasic cells the level of significance was p <0,001 and between normal cells and pre-neoplasics was pre p<0,005, that is, all differences were highly significant. However, there was "overlap" of results which does not allow its use in clinical practice.

Fung in 1975 showed that in the normal muscle type B water predominates and in muscle with solid tumor, the type A water predominates.

In 1983, Damadian showed that the water molecules of malignant tissue were characterized by an increase of osmotic mobility and therefore of water type A.

In 1996 Wiggins shows that the type A water of high-density and non-structured predominates in proliferating cells and type B water with low-density and structured predominates in cells at mitotic rest, quiescent state. The type B water in mitotic rest is converted into type A water when they start to proliferate. The author showed that switching from one state to another is an integral part of cellular function (Wiggins-1996).

Pouliquen in 2001 by MRI 1H with relaxometry studied the cytoplasmatic water in mice lymphoma, caused by poor diet in phytochemicals and rich in saturated grass acids and refined carbohydrates.

The author found the change that Felippe Jr believes that's fundamental in carcinogenesis: the decrease type B structured water in tumors. This disciplined French researcher also showed that there was decrease of structured water in serum, in the heart and in greater intensity in the liver.

The study beyond reveals a decline of the type B water in the tumor, it has shown the systemic character of cancer, that is, the body got sick as a whole; the patient has got not only the visible tumor.

It is important to stress that in 1981, Beall and Hazlewood had already written a book about the systemic effects of cancer in animals and humans showing that the patients with of tumor had changes in water behavior in both serum and in various non-tumor tissues. The T1 to the protons of water was 15 to 20% higher in normal tissues of animals with tumor when compared to animals without tumor, a phenomenon due to the systemic effect of cancer.

De Certaines in France compared the serum of 310 patients with various types of tumor in different stages of development with the serum of 224 normal controls. It verified that the increase of T1 appeared only in the final stages of the disease, however noted fact of the highest importance: in the imperceptible phase of the cancer happened a light decrease of T1 (De Certaines-1983).

VI- Activating factors and pathways of cell signaling and "oncogenes" and cytoplasmatic alkalization are secondary factors to the "stress of almost death".

In the last 40 years with the advent of molecular biology were discovered hundreds of factors (NF-kappaB, VEGF, EGF, PDGF, etc.) that are activated by an enormous range of ways of signalling (STAT3, SAP / MAPK-JNK / MAPK, ERK / MAPK, p38/MAPK), beside the activation of numerous "oncogenes" (c-fos, c-Jun, c-myc etc.).All those events are in parallel with the increase of cell proliferation, the decrease in apoptosis, the generation of neo vessels and the decline of differentiation, which led most researchers to hard study them, in search of inhibitors that were effective in treating cancer.

However, all those factors are secondary; they are resultants effects of strong mechanism of cell survival triggered by the "state of almost death" and are part of the final stage of carcinogenic process, which is cell proliferation.

The main mechanism that enabled the survival of human being on the Planet was precisely the capacity for regeneration and healing of lesions, wounds and traumatisms and these mechanisms are in the intimacy of genes from both normal cells and "malignant" cells.

In fact, there is a long time Dvorak suggested that the healing and tumor stroma shared the same properties, including vascular hyperpermeability, the leakage of fibrinogen, extravascular clotting and the presence of proteoglicans as condroitine sulphate. In the wounds and in the tumor stroma the fibrinogen is present and turns into fibrin which is then transformed into a colagenous stroma (Brown-Dvorak and Yeo-1988-Dvorak-1999).

Finally, Dauer in 2005 showed that both the wounds regeneration and cancers are characterized by cellular proliferation, remodeling of the extracellular matrix, invasion and cell migration and formation of new vessels and both tissue regeneration and cancer use common mechanisms of signalling, among them STAT 3, NF-kappa-B, SAP / MAPK etc. (Dauer-2005, Felippe-February 2004, October 2007, April 2008).

All those factors have been used by normal cells since the early days of our existence, even when we were only primitive unicellular beings. They were those factors that have enabled us to survive the extremes of temperature, the scarcity of food, rarefied air (hypoxia, acidosis), the traumatisms, the wounds, the fractures and infections (Felippe-February 2004).

The assaults with serious injury or danger of "almost cell death" activate factors and ways of signalling that protect the cells allowing that they survive the insults and the injuries. However in cancer, all of them are late and secondary elements of the process and belong to the right edge of carcinogenesis. The diseased cells and what we call malignant cells are desperately struggling to survive and they know very well put in action all the tricks of survival (Felippe- May 2003, May 2005 and October 2007).

It is also secondary the cytoplasm alkalization that provides the proper pH to cell proliferation.

Indeed, the early mitotic cell proliferation is commonly preceded by cytoplasmatic alkalization usually triggered by the stimulation of the Na+ / H+ antiporter (Tannock-1989) and by the activation of carbonic anidrases IX and XII (Ivanov-2001, Zavadova-2005).

Most of malignant cells work with the energy from the anaerobic glycolysis, which generates large quantities of lactic acid and acidify the intracellular environment. Acidic environment inhibits the glycolysis enzymes, engine of mitosis and as well as the survival mechanism the malignant cells increases the expression of elements that facilitate the flow of protons H+ to out of cells.

One of these elements is the Na + / H + antiporter and thus occurs the increase of expression of that extrusive protons bomb in the membrane of malignant cells (Barriere-2001).

Another element is the carbonic anhydrases IX and XII of natural occurrence in highly specialized normal cells which suffer significant increase of expression in malignant cells. That is what Ivanov noted in 87 types of cancer cells and in 18 solid tumors where the carbonic anidrases IX and XII were present from moderate to high quantity (Ivanov-2001). For Zavadova the expression of carbonic anhydrase IX is limited to the mucosa of intestine, but it is present in high percentage of human cancers, tissues that normally is not found (Zavadova-2005).

In the end we will have the alkalization of intracellular and acidification of interstitial liquid that bathes the malignant cells. Direct measurements show that the extracellular pH of the tumors is about 0.5 units of pH lower than the corresponding non-neoplasic tissue, which represents an increase of 50 nanomoles of H3O+ in interstitial liquid (Yamagata-1996).

Along with the increase of the expression of Na + / H + antiporter happens another mechanism of cell survival: increasing the Akt activity, protein that protects the cell apoptosis (Wu-2004). The increase of the activity of Akt blocks the cytotoxicity of TRAIL (Tumor necrosis factor-Related Apoptosis-Inducing Ligand) and increases the activity of NF-kappaB, main nuclear factor responsible in the survival of malignant cells (Ozes-1999, Chen-2001, Thakkar - 2001).

VII-Other special features of neoplasic cells

VIIa- Increase of cellular hydration

One of the characteristics of cancer cells is their water content similar to embryonic tissue of the same origin that is high. In fact, the cancer cells have consistently water content higher than the normal cells of the same origin (Winzler-1959).

Olmstead in 1966 collected in the literature several studies in which the increase of water content inside the cell is related to carcinogenesis. Meanwhile, the author did not specify the type of water that the studies above suppose to be the type A.

VIIb- Increase of cellular volume

In our hypothesis the decrease in intracellular osmolytes promotes increase of type A water. The type A water is osmotically active,

fluid and causes increase in the cell volume because the same number of non-structured molecules of A water with free molecules, that is, with hydrogen bonds scarce or absent occupy more volume than structured water type B that is osmotically inactive and viscous because it has strong hydrogen bonds that maintains cohesive the water molecules of which the most part is in the intimacy of macromolecules, proteins and enzymes and not free in the cytoplasm. It adds that the changes of conformation of the cytoplasmatic proteins due to weaker hydrogen bonds promote the inflow of water into the cells (Cameron-2005).
In fact, direct morphometric studies with computerized quantitative analysis of histological image, showed that at the beginning of mitotic cell proliferation the dimension of the cell increase. The direct measurement of the volumetric increase of the cancer cell was detected in the oral epithelium of lesions at high risk of malignant transformation (Shabana-1987) and nasal cancer mucosa induced by nickel (Boysen-1980).
In normal fibroblasts the increase of the cellular volume runs parallel with the transition from G1 initial phase to proliferative S phase of the cell cycle (Perdergrass-1991).

VIII-Life-Order-Information-Entropy

The great scientist Ilya Prigogine, Nobel Prize in Physics, has shown that a system in a state of disorder (entropy) can move to a state of order (enthalpy) if it is subjected to a considerable flow of energy.
Enunciated its concept as follows: "An open system when subjected to a large flow of energy increases the degree of order-information" Open system: it is that one where entering and leaving energy and matter: the cell (Sodi-Pallares-1998-2,000, Felippe-May 2008).
The life needs the order flow and the energy flow with the generation of inevitable wastes. To maintain the life we need an efficient system that from outside add energy and order and from inside remove the wastes.
In those conditions, disease is equal to disorder (entropy) and health is the restoration of order. We increased the flow of order through raw foods and the flow of energy through the drive of mitochondrial oxidative phosphorylation .
The energy used in all cells and that maintains the function of the organism is the free energy of Gibbs (ATP) and without it there would be no animal or plant life (the concept of free energy is more complex than above).
All the factors that decrease the production of ATP increase entropy and decrease the degree of order-information of the open thermodynamic system that it is the cell: DISEASE.
All factors that increase the production of ATP decrease the entropy and increase the degree of order-information of the cell: HEALTH.
Life is a perpetual struggle to maintain order and energy. Energy without order and order without energy are incompatible with life.

IX-The "state of almost death" changes the place of production of ATP from mitochondrial oxidative phosphorylation to the cytoplasmic anaerobic metabolism

During the evolution primitive cells passed from "Alpha" state of low energy production and high electronic saturation to the "Beta" state of high production of energy and high electronic unsaturation. In carcinogenesis happens the opposite of what happened in the evolution and the cells pass of the normal "Beta" state to the sick "Alpha" state.
The normal cells are state "Beta", the most recent of evolution: light - aerobic metabolism, where dominate the electronics unsaturation, the oxidation and mitochondrial oxidative phosphorylation. In this scheme the mechanism of survival is the cell differentiation. The engine of those cells is the mitochondrial oxidative phosphorylation and the fuel is the oxygen atoms.
The oxygen atoms are from the atmosphere, but are not forbidden to come from substances that have oxygen in their composition.
The cancer cells are in the "Alpha" state, the most archaic of evolution: darkness - anaerobic metabolism, where dominate the electronics saturation, the reduced state and cytoplasmatic anaerobic metabolism. In this scheme the mechanism of survival is the cell proliferation. The engine of those cells is the cytoplasmatic Embeden-Meyerhoff cycle and the fuel is the hydrogen atoms.
The hydrogen atoms are provided from antioxidants substances (reducing agents) as GSH, NADH, NADPH, tocopherol, ascorbic acid, and so on. .
Remembering that the ATPs generated by glycolytic cycle of Embden-Meyerhof supplies the nucleus and ATPs generated by oxidative phosphorylation don't supply the nucleus and without energy the chromosomes are immobile, they are not duplicated.
For Szent-Gyorgyi the threat of death or severe injury the cell discards the "Beta" state, discards the heavy mitochondrial oxidative mechanism and pass to the simplest "Alpha"state: anaerobic metabolism-reductor-proliferative. It is a state where dominate the electronic saturation that it is the primitive state of survival.
In fact, a great French studious of tumor metabolism affirm that the group of cancerous cells from a particular site, presents a variety of states of differentiation, ranging from highly differentiated cells, near the cell of the same origin with oxidative phosphorylation and anaerobic glycolysis almost normal and low speed of growth, up to highly undifferentiated cells with minimal oxidative phosphorylation, high anaerobic glycolysis and high speed of growth; facts that corroborate our hypothesis (Baggetto - 1992).
In fact, the normal cells in persistent suffering pass for several stages until they reach the point of proliferation.
The radiotherapy and chemotherapy are effective only in the cells in proliferation, when they reached the final stage of carcinogenesis. When they have just exterminated a certain amount of cells in franc proliferation, arrive more cells that were in the line of the process.

X- Treatments of the cancer increasing the structured type B water in relation to the type A water.

It was the ability to keep the cytoplasmatic osmolytes in a certain ideal amount that allowed the passage of life from water to land which is one of the most important mechanisms that maintain the life of the cell. We can consider it as the "Achilles's tendon" survival of any type of cell.
The strategy of reducing the amount of type A water and increase type B water of malignant cells interfering in osmolytes reaches the target, reaches the fundamental and initial point of carcinogenic process and inhibit cell proliferation, promotes apoptosis, decreases the formation of new vessels and increases the cellular differentiation. That strategy achieves the initial phase of the process of persistent suffering, reaches the left edge of the carcinogenic process.

Xa- Interstitial hyperosmolality decreases cell proliferation of malignant cells by removing from the cytoplasm the type A water

In 1988 Laboisse treated cancer cells from human colon, HT29, with polyethylene glycol (PEG) a non-toxic and not absorbable substance. PEG increases the osmotic pressure in a dose-dependent manner and removes water from the intracellular. The removed water is the type A water, which is osmotically active and thus in the cell increases the relative concentration of type B water, standard of the bioenergetic function.
In 3 weeks of treatment we can notice in the culture the emergence of cells in franc differentiation state. When submitted to subculture, those cells produce two different lineages of cells, one of them enterocitic and the other mucus secretor, both of benign character.
In 1991 Silvotti showed that the hyperosmolality decreases the proliferative response of transformed cells and almost does not interfere to the corresponding normal cells.
The transformed cells are more sensitive to the increase of the osmolality and they reduce its index of proliferation because it contains higher amount of type A water osmotically active which is removed from the cell. The decrease of type A water in cytoplasm restores partially the physiological cellular function reducing cell proliferation. If the restoration of physiological function was total, the cell would exit the "state of almost death" and the proliferation would be totally abolished, that is, proliferation now would not be necessary.
In 1991 Corpet also showed that hyperosmolality decreases malignant cell proliferation when he found that the polyethylene glycol (PEG) inhibited in a quickly and consistent way the carcinogenesis of the rats and mice colon submitted to a various types of

carcinogens. When mice drinking water with 5% of PEG and are injected with a carcinogen (azoxymethane) they decrease by 10 times the development of tumors of the colon comparing with rat control, without PEG. The administration of PEG for 16 days reduces by 5 times the tumor volume.
In fact the withdrawal of non-structured type A water from cytoplasm allows that the cell acquires its normal initial characteristics which restores the negative entropy, increases the degree of order, the metabolism becomes oxidative phosphorylation and cell proliferation no more is required. In the evolution occurs cell differentiation and "malignant" cell go to the normal way of death by apoptosis.

Xb- The increase of kosmotropo substances, that structures intracellular water has anticarcinogenic effects

The researcher Waheed Roomi and his staff at the Division of Cancer Institute Matthias Rath of California, through 13 works very ingenious brilliantly showed that the employment of a mixture of nutritional substances that structures intracellular water has anti tumor effect in several types of cancer both in vitro and in-vivo: lung, prostate, breast, pancreas, urinary bladder, glioma, testicles, melanoma and fibrosarcoma.
This anti tumoral effect includes the reduction of tumor cell proliferation, the decrease in tumor invasiveness and neoangiogenesis, the abolition of metastases and increased apoptosis (Roomi-2003, 2004 a, b, 2005 a, b, 2006 a, b, c, d, e, f, 2007 to, be Felippe - June 2008).
Roomi assigned the inhibition of metalloproteinases 2 and 9 by the effects of the mixture of nutrients. Meanwhile, that mixture has potent substances that structure the intracellular water. Then the mixture induces the normalization of cellular physiology and cellular bioenergetic and makes unnecessary the activation of metalloproteinases that open the way for the proliferation of redemptive life cancer.
The sodium thiosulfate (Na2S2O3) is a strong substance that structures intracellular water. Norbert Viallet in 2005 using only sodium thiosulfate as the structuring of the hydrogen bonds managed to reduce significantly the proliferation of human carcinoma implanted in mice.
The mice were implanted with cells of squamous cell carcinoma of human FACU and then received a single intraperitoneal injection of saline (control) or only thiosulfate (1600 mg / kg). In the saline group the tumor volume reached 1200 mm3 in 25 days of evolution and in the group with only thiosulfate reached 650 mm3, that is, there was a decrease of almost 50% of the tumor, using only one of the types of substances and in a single dose .

Conclusion

When the intracellular water changes its physical-chemical behavior and passes from low-density, osmoticaly inactive and viscous (water type B) for water of high density, osmoticaly active and fluid (water type A) the cell passes from quiescent state to proliferation state.
When increase the amount of non-structured type A water in intracellular, the cells undergo profound metabolic and bioenergetics changes with gradual reduction of the degree of order-information of the open thermodynamic system of the cell that culminate in increasing entropy. At the beginning we have just dysfunction, however, with the process evolution the degree of order-information reaches a crucial point and the cell reaches a barely tolerable level of destruction a "state of almost death" (Felippe-February 2008, May 2003).
Arriving at the "state of near death" cells discard the heavy machinery of oxidative phosphorylation and start to use the simplest cycle of Embden-Meyerhof to meet the core of ATP. In this moment it is triggering millenary mechanisms of survival and the cells start to divide and enter a state of continuous mitosis, the only way to continue living.
The normal cell when attacked is able to put into action all potential acquired in millions of years of Planet Earth to support life. The cells so-called "malignant", are "meat of our own meat" and therefore are also able to put into action all available mechanisms for survival, that is, the activation of factors and ways of signalling that: 1 - promote cell proliferation, 2 - prevent apoptosis, 3 - increase the generation of new vessels, 4 - increase the production of matrix-metalloproteinases (MMPs), etc.
They are not malignant cells, they are not cancer cells, they are only diseased cells struggling to survive. They are transformed cells in need of care, in need of treatment to return to their original characteristics in a phenomenon called cell differentiation, to walk the path to end way of death without fanfare, without inflammation, which is called apoptosis. (Felippe - May 2004, May 2005).
Finally we believe that the unsuccessful attempts of chemotherapy and radiotherapy are in the fact that such strategies attack only the right edge of the process, only in the final stages of carcinogenesis. The more rational treatment must reach the left edge of the process, in the proper early stages of carcinogenesis.

"A good idea persists until another better"
JFJ

"Stop learning is omit medical care and wait for more scientific evidence to treat it to be a scientist researcher and not a medical doctor"
JFJ

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