# Quantum Biophysical Semeiotics: Recognizing and Treating Osteoporosis, starting from Osteoporosis Inherited Real Risk.

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**Abstract.**

In the article, Author underlines that osteoporosis can involve only individuals with osteoporotic Quantum Biophysical Semeiotics constitution and Inherited Real Risk. It is generally admitted that there is no direct evidence that present screening reduces fractures. However, there is good evidence that screening is effective in identifying postmenopausal women with low bone mineral density and that treating osteoporosis can reduce the risk of fractures in this population.
As a consequence, in the war against osteoporosis we need a new clinical tool to recognize on very large scale women (and men, of course!) at high risk of osteoporosis preferably at birth, i.e., a bed-side reliable method, applicable rapidly on very large scale, which relies on the assessment of "osteoporotic constitution" and inherited osteoporotic Real Risk, based on micro-vascular remodelling, characterized by newborn-pathological, type I, subtype b), aspecific, Endo-arteriolar Blocking Devices, author has discovered and described formerly. In addition, an original theory on osteoporosis pathogenesis is illustrated, which opens new way in the primary prevention and therapy of osteoporosis, particularly when early recognized. Quantum Biophysical Semeiotics permits doctors to exclude in one second the presence of osteoporosis, even in the very initial stage of inherited real risk, ameliorating diagnostic procedure and facilitating both screening and therapeutic monitoring. Finally, diet, etymologically speaking, and treatment with drugs, which proved to be efficacious against osteoporotic ongoing, are illustrated. In this article patents based information is also included.

Key words
Osteoporosis primary prevention; osteoporotic biophysical-semeiotic constitution; osteoporotic inherited real risk; quantum biophysical semeiotics.

**Introduction.**

Osteoporosis is a disorder in which loss of bone strength leads to fragility fractures [1]. There is fair evidence to recommend screening postmenopausal women to prevent fragility fractures, no or low trauma fractures (grade B recommendation), unfortunately when disorder is already present since time [2]. Although there is no direct evidence that such as screening reduces fractures, there is good evidence that screening is effective in identifying postmenopausal women with low bone mineral density and that treating osteoporosis can reduce the risk of fractures in this population (grade A recommendation) [2].

It must be evident to all that a percentage, but not all, individuals under osteoporosis environmental risk factors suffer from osteoporosis, since the various osteoporosis risk factors may act upon osteoporosis constitution exclusively in presence of INHERITED Osteoporotic Real Risk, dependent of osteoporotic constitution, analogously to all other common and severe disorders, like diabetes and cancer, today's epidemics.

To recognize on very large scale women (and men, of course!) at high risk of osteoporosis we need, first of all a bed-side reliable method, applicable rapidly on very large scale, i.e. a method which relies on the assessment of "osteoporotic constitution" and inherited osteoporotic Real Risk, based on micro-vascular remodelling, characterized by newborn-pathological, type I, subtype b), aspecific, Endo-arteriolar Blocking Devices, I have discovered and described in previous papers, really different from the physiological types [3-17].

Such as microcirculatory pathological structures play a central role in outcome of every type of tissue preconditioning, e.g. myocardial preconditioning [29]., due to the fact that they are of pivotal importance in providing blood, i.e., Information-Energy-Material, to related parenchymal cells.

Briefly, all components of microcirculatory bed are fluctuating 6 times/minute, in a chaotic manner, regarding both the intensity and periods. These oscillations parallel those of diverse segments of urethra, doctor can bedside assess in a precise way, gathering reliable information on structure and function of related microvessels. The real measure of such as dynamics is the fractal dimension, evaluated with a lot of clinical methods of different difficulty Fig. (**1**).

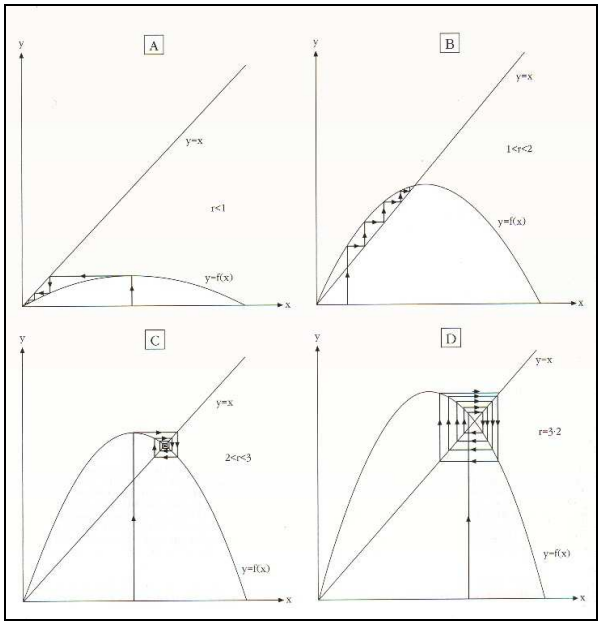
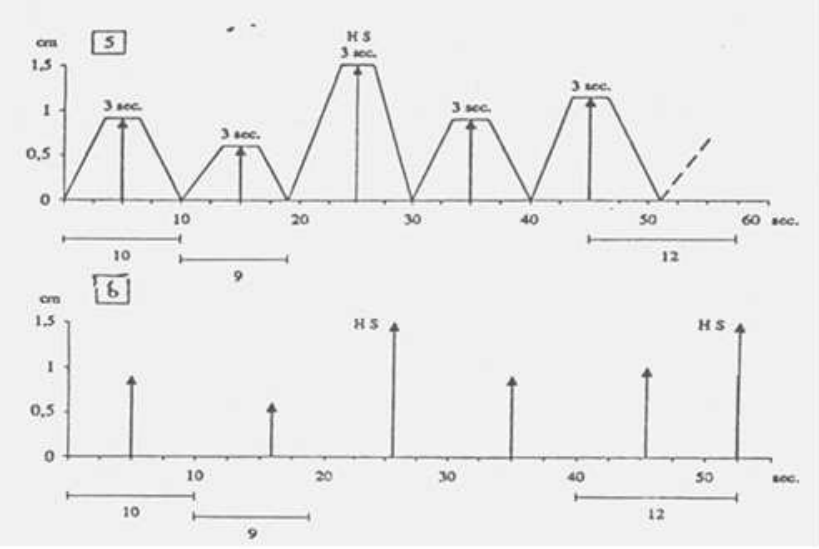



Fig. 1

The different trajectories in the phase space are clearly shown in a very elegant, refined, graphical manner. Due to the high value of 2 parameters, which varies from 0<1>4, the trajectories are attracted from a very interesting sub-space, i.e., the so-called strange attractor (d); a and b indicate a

fixed point attractor, while in c is refinely shown the closest loop attractor. (With the kind permission of Cambridge University Press, from: Peter Knight, Ottica Quantistica, pg. 324. La Nuova Fisica, Bollati Boringhieri, 1992).

The fractal correspondences of genome and the chaotic behavior of microvessels' fluctuations are well known [77], but there is an open question about how to get qualitative information from their behavior, and in order to do it we should take in account some statistic measures of chaos theory. Deterministic chaos has been defined as the 'stochastic or probabilistic behavior occurring in a deterministic system' and its main characteristics are uncertainty and unpredictability, but it is possible to detect and investigate it and to get qualitative information through invariant statistic measures such as LCE, fractal dimension and entropy. 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 it is responsible for their random appearance and unpredictability. Entropy is a measure of the uncertainty in deterministic dynamical systems, or equivalently it 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 last uncertainty about its future course, even when the dynamical rule governing the system is known with precision. Zero entropy is interpreted as the 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: no new quality information emerge for an arbitrary long interval of time. Fractal dimension is a no-Euclidean geometric measure of the orbits filling in the phase space under the action of a flow or a map, suitable for fractal objects, characterized by a non-integer dimension. While LCE and entropy are very difficult to detect in biological systems, it is possible to determine the fractal dimension of microvessel dynamics, i.e., of the microcircle, through well defined and refined QBS techniques, such as, i.e., considering the vasomotility and vasomotion diagram, and particularly taking the ratio between the highest spikes – HS (maximum points of the oscillations) and the minimal points of microvessels' fluctuation. The vasomotility and vasomotion diagram is shown in Scheme 6, where reflex's intensity expressed in cm, is on y-axis, and reflex's duration, in seconds, is on x-axis.




*Scheme 6*

In fractal geometry, the fractal dimension, *D*, is a statistical quantity that gives an indication of how completely a fractal appears to fill space, as one zooms down to finer and finer scales. There are many specific definitions of fractal dimension. We are considering in this paper the Hausdorff (1919) dimension defined as follows:

$$D = \lim_{\epsilon \to 0} \frac{\log N(\epsilon)}{\log \frac{1}{\epsilon}} \qquad (0)$$

where $N(\varepsilon)$ is the number of self-similar structures of linear size ε needed to cover the whole structure.

At this point the reader should know that it is possible to calculate, in several different ways according to style and difficulty, the QBS fractal dimension (fD) of a deterministic chaotic biological system, such as microvascular one, of any organ, tissue or viscera. Among the many procedures easily achievable at the bedside, the following is truly original: four High Spikes are emerging in a time interval of 120 seconds, dividing the space into four segments; each segment in turn, is further divided into 3 sections by two more "normal" fluctuations. Therefore, it is easy to calculate the fD of the oscillation in Scheme 6, i.e., the degree of chaos, entropy, or complexity of the figure, which roughly indicates the space occupied by the fluctuation and it is a measure of its complexity:

*(1) fD= [Ln(4) / Ln (3)] "f"*

where "f", fractal factor, is the ratio maximal oscillation (HS) / minimal oscillation.

In health "f" = 3, as previously reported, because the maximal oscillation corresponds to an intensity of the reflex of cm 1.5, while the minimal oscillation corresponds to an intensity of cm 0.5, so:

*(2) "f" = HS/minimal oscillation = 1.5/0.5 = 3*

It follows that, physiologically, the fractal dimension is $3 < fD < 4$:

*(3) fD = 3 [1.27] = 3.81*

In patients in whom a biological system evolves towards any chronic disease there is a lower fractal dimension, i.e., $1 < fD < 3$, and, finally, in chronic situations, i.e., the endocrine pancreas in diabetes, fD is tending to 1, the topological dimension.

QBS is able to provide through the auscultatory percussion of the stomach and by means of chaos theory's tools very useful study cases about several diseases or potential pathologies as, i.e., in the following example about Oncological Terrain and Inherited Real Risk of cancer.

| ***Fractal Dimension*** | ***Equilibrium*** | ***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 ≤ fD < 3* | *limit cycle* | *initial implementation of the tendency to disease /potential pathology- i.e. Osteoporotic Constitution – initial evolution to disease* |
| *3 ≤ fD < 3.81* | *limit cycle tending to strange attractor* | *tendency to physiologic condition (only potential phase)* |
| *fD ≥ 3.81* | *strange or chaotic attractor* | *Physiologic condition – healthy state* |

*Table 2*

*Legend: the fractal dimension (fD) is calculated as the time of the disappearance of gastric aspecific reflex, before the appearance of the next one. It is important to state that the fD is directly related to (d) or inversely (INV) related with:*
*A) (INV) the local Microcirculatory Functional Reserve – MFR - (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) (d) with the duration of the gastric aspecific reflex*

A 52-year-long well-established clinical experience allowed me to suggest such as clinical method as well as an original theory on osteoporosis pathogenesis. Interestingly, a congenital functional mitochondrial cytopathology, I called Congenital Acidosic Enzyme-Metabolic Histangiopathy (CAEMH) represents the "*conditio sine qua non*" also of osteoporosis [3-7, 18-20].
Moreover, all patients affected by impairment of collagen metabolism of whatever nature, as well as location, including perivascular GAG, I visited in the past three decades, were or are CAEMH-positive. As a consequence, mitochondrially altered cells, even from the functional view-point, due to low endocellular free energy, become a-social elements causing possibly the most common human disorders, referred above.
Interestingly, with the aid of Quantum Biophysical Semeiotics (Bibliography in my website: www.semeioticabiofisica.it), doctor can easily recognize at the bed-side and "quantify" the osteoporotic inherited real risk, present always in individuals with CAEMH-dependent, osteoporotic constitution, as well as overt osteoporosis. In fact, such as original physical semeiotics allows doctors to bedside diagnose, in a few seconds, also osteoporosis since its early stage. Quantum Biophysical Semeiotics, although very useful at the bed-side, is now-a-day, unfortunately, mainly overlooked. In a few words, from practical view-point, in health, due to no local real in biological systems “intense” digital pressure stimulation of whatever bone (e.g., radius-ulna) does not cause gastric aspecific reflex.
On the contrary, in individuals with osteoporotic constitution or overt osteoporosis, such as bone stimulation brings about simultaneously gastric aspecific reflex, whose intensity parallels the seriousness of underlying disorder Fig. (**2**). In addition, soon thereafter, “mean”digital pressure, e.g., applied on lumbar or caudal vertebrae (= spinal process), provokes the Gastric Aspecific Reflex after a latency time of 8 sec. (= in the stomach both fundus and body are dilated, while antral-pyloric region contracts). Interestingly, bone “preconditioning” (= after 5 sec. exactly doctor performs a second examination) brings about latency time increasing: 16 sec. On the contrary, in both osteoporotic constitution or real risk and osteoporotic patient, basal latency time is 8 sec. and

respectively < 8 sec., in relation to underlying disorder severity. In fact, bone preconditioning appears to be pathological, i.e. shorter than the basal one (www.semeioticabiofisica.it/Documenti/Eng/Precondizionamento%20semeiotico_eng.doc) .
In this report, I illustrate a new, really efficacious, primary prevention and therapy of osteoporosis predisposition, initiated preferentially since birth or in young age, based on correct diet, ethimologically speaking, like Mediterranean Diet, Ubidecarenone cycles, Conjugated Melatonine, physical exercises and avoiding tobacco smoke, in a personalized manner, under bedside therapeutic monitoring [3-7, 15, 18-20].

**Quantum Biophysical Semeiotics Constitutions.**

A) **A necessary epistemological consideration**.

Apart from its inflammatory, infective, degenerative, metabolic, Oncological nature, whatever disease arises and shows a course in relation to individual *constitution*, since environmental factors, certainly determinant, interact with genetic factor, always present.

On the other hand, there is clear evidence of causal links between food and nutrition and osteoporosis sufficiently strong to be a basis for recommendations to policy-makers and to the general public. In fact, it is now apparent that, although genetic predisposition varies, the key factors determining whether or not people develop osteoporosis are environmental

At this point, let us consider the primary role played by the *constitution*, evident in all diseases, including those of early childhood, viral in origin, whose course is influenced, although not exclusively, by psycho-physical condition of involved subject.

Without any doubt, *genetic, constitutional factor* shows its primary role in degenerative, metabolic disorders as well as in chronic inflammations and in malignancies, as I demonstrated previously [3].

It is now generally admitted that the "genotype" affects onset and course of all most frequent and severe human diseases, maybe interacting with environmental factors, as it is clear that "without rice-field the rice does not grow up" [3-5].

On the other side, due to our *forma mentis*, characterized by an outlook on reality where *thesis* and *antithesis* end in a superior *synthesis*, i.e. both polarities converse in a useful dialogue, in case of pathology we neither feel difference, nor contrast and conflict between *genotype* and *environment*, which are prone to be harmonized, in our mind, as all series of *thesis-antithesis*, according to eastern wisdom. In other words, rather than mechanistic determinism and Cartesian dualism (Mars), based on the *vision epistemology*, according to M. Serres (Lucrezio e l'origine della fisica, Sellerio, Palermo), we prefer clearly the nature philosophy (Venus), based on *contact epistemology*, that allows us to gather those qualities (properties) overlooked by the classic science in favour of quantity. "A nature seen, heard, full of emanations, fragrances, noises, bitterness and saltness" (Serres) .

From the *solid* of classic science we pass to *fluid* of non-equilibrium thermodynamics, which is more close to the reality. We hint at *deterministic chaos* as well as **concursus oppositorum**, that helped us to better understand that nature, in which we take part, as Proust says, although we do not know it.

Finally, we support the *global, holistic vision* of both man and reality, in which he takes part, firmly persuaded, however, that "the map is not the territory", as we have written earlier [3].

B) **Clinical definition of the Quantum Biophysical Semeiotics Constitutions**.

In order to define clinically osteoporotic constitution, and the related Inherited Real Risk - IRR, which does not exclude the presence of other ones, it is necessary to think over the current possibility of gathering at the *bed-side* quantum-biophysical-semeiotic – QBS - data rich of biological and molecular-biological information on the various human organs, tissues and apparatus, so that doctor can recognize numerous types of *constitutions*, often associated.

Without any doubt, these data can not be observed by the aid of traditional physic semeiotics, unable of carrying molecular-biological events to clinical dimension, which really represents the most original and fertile aspect of **Quantum Biophysical Semeiotics** [3-15].

After these unavoidable preliminary remarks, we must think that the *genome* notoriously contains all necessary information for individual development and preservation: a mutation, a change, an alteration of refined and articulate processes of mit-DNA and n-DNA reparation, a brake or a stimulation of some genes action can bring about osteoporosis, tumour or other diseases or promote their onset, under particular environmental conditions, which are surely of paramount importance: See later on.

The "clinicians", who now-a-days are becoming rear, hold out against their extinction – we are proud to be considered "clinicians" – do not take any interest neither in "direct" understanding of molecular-biological events on the base of genomic processes, nor in everyday discovery of genes mutation, supposed causes of different diseases. However, we "clinicians" think that whatever event of such origin, is followed by and associated with other events, which reveal themselves in a different dimension, e.g., biological at *tissue-microvessels* level, now convinced and persuaded by our observations, gathered in a 55-years-old experience at the bed-side, that both *parenchyma* and respective *microvessels* are tightly related, both functionally and structurally, far beyond the well-known Tischendorf's concept of *Angiobiotopy* [3-7,16].

In short, in order to clarify exactly our concept we are going to use an analogy, which represents not only a "form" of thought, but also a "structure": ″we "clinicians", due to both calling and choice, do not worry about the water of Alps maintains before it flows along its river-bed, but prefer analyse it starting from the first banks during its slow growing to develop as a river, and then evaluating it with unfailing patience until its complete ripening down to the plain, and, finally, observe all its characteristics near the mouth ″ [3-7].

Due to these fundamental reasons, **Krogh** was right: "the study of microvessels nowadays shows fortunately its original, essential, and favourable influence on the evaluation of all tissues and biological systems, including obviously macro-as well as micro-circulatory system, under both physilogical and pathological conditions" [3].

A lot of years ago, for the first time clinically I have investigated the interesting relations between *parenchyma* and *microvessels* in the central nervous system [17,21-24], and have demonstrated at the bed-side the perfect "symmetry", in healthy, between these two biological sub-systems: for instance, if an individual "is thinking" to move (or, moves, of course) a finger or a toe, immediately appears, although for a limited time, microcirculatory activation, type I, associated, at level of the related parietal neuronal motoric centre (See later on). On these events is based my Angiobiopathy theory, a fundamental clinical tool in describing and bedside recognizing biophysical-semeiotic constitution and relative inherited real risk.

However, at this point, it is interesting to say that limited parenchymal hyperaemia (more precisely speaking, "microcirculatory activation type I, associated", characterised by vasomotion increasing of both arterioles and small arteries, according to Hammersen, and capillaries as well as post-capillaries venules) aims to maintain the physiological cell activity in tissue areas initially suffering, showing, once again, the perfect relation between *parenchyma* and *related microvessels*. Exclusively in case of overt disease appears the phase of "microcirculatory activation type II, intermediate, and thereafter the dissociated form, type III". The so-called "microcirculatory failure" indicates the final stage of microcirculatory insufficiency.

This is the umpteenth evidence of internal and external coherence of biophysical-semeiotic theory, useful to demonstrate that we are moving in a faultless manner, from the methodology view-point, also in meeting this specific problem of primary importance in order to define clinically the diverse *constitutions*.

"How does the *genome* (n-DNA and mit-DNA) influence both function and structure of the *microvessels* and consequently, the *microcirculation* of related biological systems, in physiology as well as in pathology?"

C) **From genotype to tissue-microvascular system.**

The starting point – *Anfangspunkt* – of my thought is the "intuition" that the *genome*, through molecular-biological events not completely known (mit-DNA and n-DNA helix opening, mRNA synthesis, proteins synthesis, a.s.o.) controls formation, development and maintenance of *parenchyma*, but simultaneously and unavoidably acts fundamentaly, in direct and/or indirect way, on the structure as well as function of related *microvessels*, according to Sherrington's statement, as regards the brain and the structural-functional relation between *tissue* and related *microvessels* (2, 3, 4, 5, 6).

Based upon such as "intuition" (initial and metaphysical moment of all scientific epoch-making discoveries), *genome* information are transferred to both *parenchyma* and related *microvessels*, including the so-called *vasa vasorum*:

**genome**

⇓ ⇓

**parenchyma** ⇔ **microvessels**

When this "intuition" is accepted, although in a transitory manner, as theory 0, immediately and unavoidably a second, fundamental question is asked.

"How does the *genome* interfere on development and maintenance of tissue-microvascular sub-system of the various biological systems ?".

In health, *genetic* information provides notoriously the necessary directions to formation, repair and maintenance of every microvessels sub-systems, which nowadays can be studied and assessed at basal line as well as by means of dynamic stress-tests, also clinically [3-20]

It is well known and generally admitted that "The map is not the territory", but due to a precise *map* we are able to gather useful information on the *territory* in order to foresee a lot of things, e.g. in our case, about tissue-microvascular system: an health microvascular bed show a structure, we know almoust entirely, which can perform distinctly a functional activity, deeply illustrated from the clinical point of view, in both "static" and "dynamic" manner [3-17, 21-27].

In health, when the *parenchyma* necessitates greater energy supply, due to whatever cause, e.g. during simulation tests (effort simulated test, as above referred), suddenly provokes the activation of refined mechanisms at the base of Microcirculatory Functional Reserve (MFR), which notoriously aims to parallel actual tissue demand of matter-energy-information, even rapidly increased, by means of microcirculatory activation type I, associated.

We realize at first, then think in a logical way, and finally foresee that eventual modifications of *genome* informations, brought about by mutations or other modifications, appear necessarily on two directions, as biological-molecular events at *parenchymal* level as well as at *tissue-microvascolar* level, as indicated in the above-illustrated scheme.

According to the utmost exactitude of the rules of deduction logic, from the above statements, we consider as impossible supposition the presence of a healthy *tissue-microvascular* system associated with a *parenchyma* at least actually "potentially" diseased, although the microvascular alteration could be localized in a very small area and not at all systemic.

In other words, we "conjecture" that wrong *genetic* information, apart from its causes, influences unavoidably both *parenchyma* and related *microvessels*, independently of the nature and seriousness of altered informations, "even" in all respects of well-known Tischendorf's concept of *Angiobiotopie*, which states that the *tissue-microvessel sub-system* is related to its *parenchyma* as far as structure and function are concerned, as demonstrates, for instance, both function and structure of microvessels in a sclerotic tissue: a great number of arteriole-venous anastomoses, functionally speaking, and a few of *nutritional capillaries*.

According to our phylosophy, i.e. critical-dialectical-analytical realism , and to successful and revolutionary "horizontal" thought, according to De Bono, after the initial metaphysical moment, in scientific discovery it is necessary to go on in a strictly deductive-logical way, based on the logic of no-contradiction as well as of *internal and external coherence*, which does not certainly coincide with the truth, but represents without any doubt the necessary condition.

Once again, starting from "intuitive, axiomatic, and apodictic" introductions, temporarily accepted as true, we proceed with the aid of deductive logic and finally formulate "empiric" statements, which can be falsified o provisionally corroborated, confronting them with clinical reality [3].

D) **Microangiology of Quantum Biophysical Semeiotics Constitutions.**

At this point, we are able to assess separately the **QBS constitutions** from the clinical microangiological point of view, underlining eventual characteristics, firstly saying that various patterns, which will be described later on, differentiate each other and result necessarily different, and appear easily recognizable at the bed-side, although they are only variations of identical theme. It follows that it is impossible to draw an unique clinical microangiological model of biophysical-semeiotic constitution, fit for various disorders different each from other as far as origin, nature and pathogenesis are concerned, although their basis is practically identical.

For instance, let us think likeness-difference, as regards clinical microangiology, among hypertensive constitution (*pre-hypertension stage*) [27], on the one hand, and *diabetic constitution*, on the other hand (*pre-diabetes stage*), where histangi*u*m alterations are common, but those pancreatic, hepatic, and of adipose tissue are present exclusively in the later.

In actual fact, as we often remembered it, like the most severe human diseases, osteoporosis may arise only in individuals involved by osteoporotic constitution, CAEMH-dependent, which represents the *conditio sine qua non* of all human severe disorders, and is certainly the genetic link, I have clinically demonstrated many years ago [18-20].

It is easy to show the "link", genetic in nature, between the most serious human diseases, i.e. CAEMH-$\alpha$ [3-5, 18-20, 28]. Really, it is not at all easy to illustrate briefly the "differences", which characterize genomic expressions on clinical-microangiological dimension as regards **Quantum Biophysical Semeiotics**. Consequently, we must go on with logic evidence, and describe, without opposing them but exceeding them in the synthesis, general concepts as well as particular aspects at the base of our interpretation of microangiological constitutions or inheritance.

In other words, in a group of patients CAEMH-positive, comparable each other as regards age, sex, basal disease (flu), socio-economic conditions, a.s.o. fortunately we observe a certain number with *predisposition* to osteoporosis.

Therefore, it is a matter of assessing the difference, which is *ruled by genome*, molecular-biological in nature, certainly existing between the two women sub-groups (or men, although less frequently), only seemingly equal, in order to obtain hopefully the definition of **osteoporotic constitution.**

The presence of rheumatic disorders in the same family and the frequent association of various rheumatic diseases in the same individual (CREST), and, on the contrary, the absence of these disorders in other subjects of well-defined family groups suggest the existence of such condition.

At this moment, it is necessary to remember and underline a really interesting data, which corroborate the scientific truth of QBS theory, **osteoporotic constitution** maternally inherited as all mitochondrial disorders, is based on. Therefore, clinical evidence corroborates the scientific values of my interpretation, illustrated in some papers [3-17, 21-27, 18-20].

In reality, clinical evidence underlines the general validity of our interpretation of initial *intuition* of the contemporaneous *microangiological* manifestations, that can be assessed at the bed-side in "quantitative" manner, of genomic information, even when it is the side of mutation or of whatever different alterations, until now revealed notoriously by means of *parenchymal* modifications and, of course, of genome itself, by very sophisticated methods. Parallel considerations are to be shown for **osteoporotic constitution** [4-15].

A further clinical evidence, which upholds biophysical-semeiotic theory, is represented by the type of *abdominal adipose tissue microvessels* (but not that of "peripheral" adipose tissue) in individuals at "real" risk of *dyslipidaemia* and subjects actually health, who in the past time have suffered from cholesterol, total and/or LDL and/or triglycerides high blood levels.

In a long and well established experience at the bed-side, we have observed that in "all" these individuals, without exception (from epistemological point of view, the statement "all" is really full of both informations and scientific value, due to the fact that it could be easy falsified), doctor observes always a characteristic alteration of Endothelial Blocking Devices (EBD) (See later on), i.e. opening duration, assessed as duration of mean ureteral reflex (= dilation of the mean third of urethra: See, Technical Page, N° 3, in www.semeioticabiofisica.it) during stimulation of "middle" intensity of related trigger-points by lasting pinching of lateral abdominal skin, is < 20 sec. (NN = 20 sec.), and closure duration, i.e. duration of reflex disappearing, is > 6 sec. (NN = 6 sec.).

From hemorheological point of view, such situation coincides with lowering capillary-venous blood-flow, showing local parenchymal alteration. This *microcirculatory* modification precedes by years or decades the onset of *dyslipidaemia*, which obviously can be "potential", i.e. without becoming clinically evident, if the individual undergoes a correct diet, etymologically speaking.

The reader comprehends certainly that there are very numerous evidences, similar to those above briefly illustrated, that corroborate our "intutition" as regards the *microcirculatory* aspect of the diverse **constitutions** and of their pathogenetic interpretation, i.e. as consequence of genome action on structure and function of the *tissue microvascular units* of different biological systems, and not only on related *parechyma*.

At this point, if the various QBS **constitutions** really exist, the problem that we face is how can we recognize them at the bed-side, namely with the aid of the new physical semeiotics. This will be the topic of next articles.

## E) **The central role played by newborn-pathological Endoarteriolar Blocking Devices in recognizing biophysical semeiotic constitutions.**

The impairment of blood-derivative structures, i.e. arterio-venoular anastomoses and particularly Endoarteriolar Blocking Devices (EBD), which control the blood-flow along capillary bed, and particularly EBD, type II, ubiquitous, allow doctor to make easily bed-side diagnosis of hereditary microcirculatory disorders (genetically ruled by), in day-to-day practice: for instance, in individuals at birth, utilizing biophysical semeiotic *preconditioning*, a really useful clinical tool, easy and rapidly to apply, permits doctor to recognize the altered genetic information in organs, tissues, even in their very small areas, as in a mammalian quadrant (*Preconditioning*: after 5 sec. exactly of

interval from basal evaluation of numerous parameters value, doctor assesses for the second time the identical parameters. In healthy, the value ameliorate clearly, while in patients they persist unchanged - pre-pathological stage or initial phase- or worsen clearly, in relation to the seriousness of underlying disorder.

In fact, the result of *preconditioning* is related to the structure and function of local *microcirculatory bed* – Microcirculatory Functional Reserve (MFR) – since it is related to anatomo-functional impairment of a part of local microcirculatory system, that indicates the altered genetic information, causing pathological changes of activation of MFR of different severity during *preconditioning* and consequently bringing about the pathological result.

An easy method, reliable in bedside recognizing **osteoporotic constitution,** that can evolve to clinical disease, is the following: in health, mean-intense digital pressure on IV-V vertebral spine brings about small (less than 1 cm.) gastro aspecific reflex, after a latency time of 3 sec. which increases after 10 sec. exactly. On the contrary, in case of **osteoporotic constitution, the first reflex results intense (1 cm. or more) and it augments after 9 sec. Fig. (**2**).**

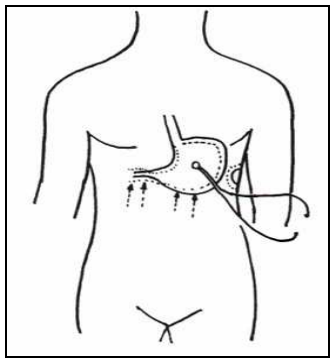


Fig.(2). ***Lines, upon which digital percussion must be applied, directly and gently, from outer side towards the bell-piece of stethoscope, in order to perform Stomach Auscultatory Percussion, are clearly illustrated.***

Really precious is QBS *preconditioning* of lumbar vertebrae in osteoporotic constitution: after 5 sec. exactly of interruption, i.e., after first examination, doctor evaluates this reflex a second time: physiologically, lt. increases to 16 sec. or more, lasting less than 4 sec. (= normal MFR, indicating absence of pathological EBD). On the contrary, in subjects with osteoporotic constitution, *preconditioning* shows pathological results, of different severity in relation to the degree of underlying metabolic disorder: basal latency time of reflex appears to be $\leq$ 9 sec. (NN = 10 sec. age-dependent) and soon after *preconditioning* it appears increased slightly.

At this point, the accurate investigation into the microcirculatory vessels of these organs and viscera allows to show an very interesting fact, i.e. the congenital modifications, both structural and functional, of EBD, as I referred above – duration of mean urethral reflex Fig. (**2**), which parallels EDB opening, < 20 sec. (NN = 20 sec. precisely) and closure duration > 6 sec. (NN = 6 sec.), demonstrating the primary role played by these worthwhile haemoderivative structures, which unfortunately are nowadays little known or overlooked. Finally, the presence of newborn-pathological, subtype II, type I EBD plays a paramount role in detecting osteoporotic constitution.

The above detailed description is unavoidably necessary to diagnose osteoporosis since its initial inherited stage, unrecognized until now with the aid of sophisticated, expensive, laboratory and image semeiotics [29-34].

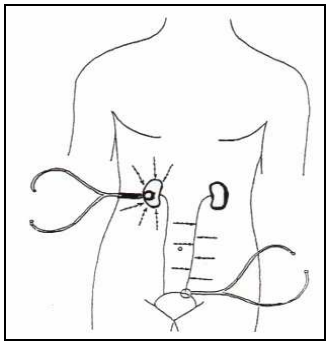


**Fig. (3)**. The figure shows the proper location of bell-piece of stethoscope, and lines upon which digital percussion must be applied, directly and gently, towards the bell-piece of stethoscope, in order to perform kidney and ureter Auscultatory Percussion, in order to assess ureteral reflexes and their fluctuation.

**Coenzyme Q10 in Osteoporosis Therapy**

It is now timely to increase research on the projected clinical benefit of Coenzyme Q10 (CoQ10) to treat diseases other than cardiac disease. Abundant data in present literature underline the benefits of CoQ10 in different disorders, and especially, as I have demonstrated for the first time, in osteoporosis therapy [35-41]. Since all common and serious human disorders are based on CAEM, a maternally inherited mitochondrial cytopathy, ubidecarenone utilization in treating osteoporosis is justified on the ground of its central action mechanism. Therefore, we must be careful that critics do not label CoQ10 as a "cure all", but understand that essentiality of bioenergetics to life functions is a sound rationale for the therapeutic benefit of CoQ10 to diverse diseases [35-41].

Ubiquinone is present in all tissue cells, and in a large number of vegetables, in variable amounts, so that a proper diet, like Mediterranean Diet, prevents CoQ10 Deficiency Syndrome [35, 38-41]. At this point, I have demonstrated the benefits of a diet containing fish, i.e. omegra-3, since they augment CoQ10 tissue level, and activate CoQ10 mytochondrial cycle [35].

However, nowadays, due to diet modifications and the use of some drugs, as statines, Ubidecarenone deficiency is more frequent than generally admitted [38, 40-2]. In fact, it is highly likely that statin-induced myopathy is the result of an acquired coenzyme Q10 deficiency in some individuals, but not in all patients, according to my theory of Single Patient Based Medicine [3-6]. However, Coenzyme Q10 supplementation alone does not reverse the condition in everyone. There are at least two possible explanations for this. First, statins could unmask a latent or initial, symptomles, metabolic disorder. This has occurred with other drugs, e.g., Fibrates, which have caused worsening of symptoms and higher CK levels in patients with known postpoliomyelitis syndrome and Mc Ardle disease [43].

Up till now il has been possible to demonstrate Coenzyme Q10 deficiency by its plasma and platelets assay, measuring platelets mithocondrial enzymatic activity or using sophysticated methods as miocardial and muscle biopsy.

This diagnostic approach is not easy to manage by the General practitioners, therefore the diagnosis of CoQ10 deficiency is almost always delayed and delegated lo the specialists. Thanks to my discovery, now Coenzyme Deficiency Syndrome is rapid, clinical and reliable. In fact, in a long clinical experience it proved to be helpful to the general practitioners either from the clinical, diagnostic view-point than for monitoring the results of therapy [7, 38-41].

The present understanding of the central bio-energetic role of CoQ10 in mitochondrial redox metabolism and phosphorylation of ADP has now well demonstrated [35, 38, 44].

Analogously to Conjugated-Melatonin multiple action mechanisms, Coenzyme Q10 ameliorate mitochondrial function, impaired in some biological systems in individuals positive for CAEMH.

As a consequence, the use of both drugs has proved to be, in my experience, really efficacious in a lot of disorders, including osteoporosis, especially when administered in earliest stage, i.e., in individuals apparently healthy, but positive for osteoporosis inherited real risk [35, 38, 41].

**Modified Mediterranean Diet Central Role in preventing Osteoporosis.**

The association of diet with several diseases has attracted since ever much attention among Authors. Recently, interest has concentrated on dietary patterns, because they can accommodate the complex interplay of nutrients within a diet. Dietary patterns have often been studied in relation to the mortality of elderly people, because of interest in this important age group and because of methodological considerations, for example, the cumulative effects of diet over an extended period and the high frequency of deaths [45-47]. The Mediterranean diet has been used in many studies because several of its components have been related to common chronic diseases, and ecological evidence suggests that such a diet may be beneficial to health [47], and variants of this diet have improved the prognosis of patients with coronary heart disease [48].

The modified Mediterranean diet is characterised by a high intake of vegetables, legumes, fruits, and cereals (in the past largely unrefined); a moderate to high intake of fish; a low intake of saturated lipids but high intake of unsaturated lipids, particularly olive oil; a low to moderate intake of dairy products, mostly cheese and yogurt; a low intake of meat; and a modest intake of ethanol, mostly as wine [45].

Intake of calcium, the major mineral constituent of bones, unavoidable in osteoporosis primary prevention in people involved by osteoporotic constitution, largely reflect the patterns of intake of foods that are good dietary sources. Novel vitamin D analogues are useful for the prevention or treatment of bone disorders such as osteoporosis [49].Calcium is found in food of both plant and animal origin. Admittedly, reach sources are dairy products, such as milk, cheese, yoghurt, and small fish, particularly in their bone. Citrus reticulata plant extracts are useful for the treating osteoporosis is discussed by Patell and Avestha in WO2008004026 patent [50]. Parmacuitically isoflavone containing compounds are used for the treatment of osteoporosis and inflammatory joint disease is patentes by Dillaha and Adams [51]. Calcium is central to a variety of functions in the body, such as nerve and muscle activity, as well as bone metabolism. In addition, osteoporosis is seen by the authors as an outcome of calcium deficiency, in that such as deficiency may lead to the development of a lower peak bone mass. Unfortunately, not all physicians know Quantum Biophysical Semeiotics, and thus ignore biophysical semeiotic constitutions and related congenital real risks.

Briefly, adherence to a Mediterranean diet proved to be efficacious in preventing most common and serious disorders, also in personal experience, particularly if personalized, and modified, after therapeutic monitoring.

Interestingly, Trichopoulou's fascinating study comprises a very large number of participants: 74.607 men and women, aged 60 or more, without coronary heart disease, stroke, or cancer at enrolment and with complete information about dietary intake and potentially confounding variables were enrolled in this Multicentre, Prospective Cohort Study, according to EBM [46].

However, we have to care an "unique" individual, a "single patient" with particular biophysical-semeiotic constitutions, Single Patient Based Medicine is based on. In fact, we must consider accurately in the "single" patient its (her) entire biophysical semeiotic constitutions (dislipidaemic, diabetic, hypertensive, gouty, osteoporotic, and particularly Oncological, i.e., Oncological Terrain) [3, 5, 6, 11-13].

Accordingly, also my 52-year-long clinical experience, since I am living in a Mediterranean country (Liguria), allows me to state that such as diet, in general, was associated with increased survival among older people, especially when modified adding to it unsaturated acids and omega-3, and suggesting physical exercise, walking about 40 min. day. As a matter of fact, independently of

criticism, more or less constructive, really sometimes absurd, which derives from crass, a-critical acceptance, due to blinkered doctor's attitude, of a paradigm of EBM, teaching this theory has surely benefit by its practical application. In my opinion, however, to reach further and remarkable advantages in clinical decision, therapy, in programming clinical researches, primary prevention, and to avoid useless procedures we must know sense and significance of microcirculatory remodelling, characteristic of inherited real risk of osteoporosis and other common disorders [4-6, 14, 15, 52]. I intend the term "diet" in etymological sense, including, e.g., daily physical exercise, whose paramount importance I briefly highlight in following, since it works ameliorating endothels function, as does Conjugated-Melatonin, according to my earlier articles [4-6, 53].

The endothelial cells, mechanic-responsive, play a paramount role in highlighting some overlooked action mechanisms of physical exercise. Exposure to shear stress or stretch results in a range of electrophysiological, biochemical, and gene regulatory responses that, if the stimulus is sustained, often result in predictable changes of cell morphology. So, for example, unidirectional shear stress elongates endothelial cells in the direction of the shear in a force- and time-dependent fashion, whereas stress applied at a highly variable frequency, duration, and magnitude (e.g., in turbulence) induces a polygonal morphology without preferred orientation.

*In vivo,* cells align with the flow in region where the flow is unidirectional. In contrast, morphology abruptly changes to polygonal at the border of flow separation regions where recirculation is created and where the shear stresses vary in direction and magnitude throughout the cardiac cycle. When endothelial cells are subjected to mechanical stimuli, diverse responses are generated, some of which are extremely fast, while others develop over hour or days. Rapid changes in ionic conductance, inositol triphosphate generation, G-protem activation, and intracellular free calcium in response to stresses occur. Many of these rapid responses are similar to second-messenger responses that result from agonist-receptor coupling, and this suggests that the mechanical and agonist responses may share common transduction pathways [54,55]. In conclusion, physical exercise acts favourably on endothelial function, among shear stress, beside interesting cytokine production, as adiponectin, which acts favourably on bone metabolism (See later on).

**What we need to know about Melatonin Action Mechanisms in Bone Metabolism.**

In former paper, I have described new action mechanisms of melatonin [6]. Moreover, in an ongoing research (data not jet published) melatonin proved to be really useful in ameliorating bone calcium metabolism in humans, as demonstrates also the following experimental evidence: when healthy individuals closes his (her) eyes, "simultaneously" calcium absorption in the bone increases in a significant way, i.e., there is bone microcirculatory activation type I, associated, and interstitium is smallest (= "in toto" urethral reflex), indicating the absorptive state. My data corroborate those of a lot of researches, carried out by Authors in both animals (rats) and humans [56-60,54]. In fact, these research results suggest that pinealectomy in rats and long-term melatonin administration significantly influence circadian metabolism of bone tissue and an important role in the mechanism of this dependence seems to be played by the changes of endogenous melatonin concentration. A possible mechanism of this relationship might involve, besides calciotropic hormones, IGF-I, corticosterone and FT3 concentrations [56, 57], particularly, both a direct action on bone metabolism, and the stimulation of adiopnectin secretion [5, 6, 53]. Bone resorption disorders are also discussed by Olsen and Ueki in WO2008048466 patent [61].

The results obtained by other Authors indicate that melatonin treatment restrained bone remodelling after ovariectomy; the effect of melatonin required adequate concentrations of oestradiol; melatonin augmented oestradiol effects on bone in ovariectomized rats; a counter-regulation by melatonin of the increase in body fat caused by ovariectomy was uncovered [58]. Combination of estrogen agonists and sodium fluoride are useful for the treatment of bone disorders including osteoporosis [62].

Kesemenli C, S, and Necmioğlu hypothesize that in the case of an individual with a head injury, melatonin can enhance osteogenesis [59]. In virtually all species to date whether nocturnal or diurnal, melatonin is synthesized and secreted during the dark phase of the day. In traumatic subarachnoid hemorrhages, in the hypothalamic syndrome, the melatonin content was very high in liquor [59]. Osteoblastic activity rises with the increase of melatonin in the same research, according to my above-referred data. Healing of a fracture of long or large bone can often be accelerated in patients with severe traumatic brain injury. Melatonin might cause early bone healing and hypertrophic callus [59].
Interestingly, as I demonstrated in humans from the "clinical" view-point [3-5], the two subtypes of retinoid Z receptor (RZR αand β) and the three splicing variants of retinoid orphan receptor (ROR α 1, α2, and α3) form a subfamily within the superfamily of nuclear hormone receptors [59]. Very recently has been demonstrated that the pineal gland hormone melatonin is a natural ligand of RZRα and RZRβ [3, 5, 59]. Ligand-induced transcriptional control is therefore proposed to mediate physiological functions of melatonin in the brain where RZRβ is expressed, but also in peripheral tissues, where RZRα was found [59].
In my opinion, such as action mechanism of melatonin in ameliorating bone calcium metabolism is more complex than generally admitted, including also the positive effect on adiponectin synthesis in lever, and parietal wall. As a matter of fact, adiponectin have showed a protective effect on bone metabolism in patients with type 2 diabetes mellitus [63], corroborating my results in individuals with predisposition to osteoporosis [3, 5, 59] and under different conditions [64, 65].

**No local Realm in Biological Systems: fundamental Role in rapid diagnosing Osteoporosis since initial Stages.**

I demonstrated that in all biological systems, of both human and animal, besides local realm, there is no local realm, wherein space/time matrix is jet quadrimensional, but showing 2 S/D and 2 T/D, characterized by a different type of information. As Lory's Experiment demonstrates, under such circumstance, information is "simultaneous", without spending time end energy [66, 67]. In a few words, information appears "simultaneously" in a human body, even in those located kilometres away from information origin.
To summarize, the communication between biological systems, also with aliens, if possible, can be realized exclusively by the aid of quantum physics, and thus utilizing the characteristic IE of the no local realm, as I have been doing since November 2007 in diagnostic field [68, 69].
At this point, I refer to a recent (August 5, 2008), singular, endocrinological, clinical diagnosis: a woman 53 year old, in Florenz, involved by recurrent renal colik-like pains, performing my advice (instructions) sent by phone from Riva Trigoso (Genoa), was applying digital stimulation separately on the 4 parathyroid glands trigger-points. When she stimulated right, inferior gland, I was able to recognize Parathyroid Adenoma, since type I, associated, microcirculatory activation in myself!
The diagnosis has been corroborated three days later in my office, and subsequently by laboratory and echtomography data (Parathormone blood-level 108 ng.; NN = 8 ng.).
The above remarks account for the reason that physicians are able to exclude whatever biophysical-semeiotic constitution in one second. A part from the positive influence in diagnosing, this medical advances proved to be efficacious in selecting rationally individuals to enrol in Osteoporosis Primary Prevention, as well as of other common and serious disorders, today's epidemics, like osteoporosis, diabetes and cancer.
Really, one cannot understand the real reason why the numerous predispositions to diseases (i.e., Biophysical-Semeiotic Constitutions), and relative inherited real risks, recognized with a stethoscope since birth, although accepted and spread among physicians by the majority of famous peer-reviews, are not suggested to physicians by National Health Services.

In addition, traditional Medicine cannot highlight a lot of biological events, as Lory's Experiment, because it knows exclusively the Local Realm in biological systems. Really, in all tissues - besides that - it exists also non local Realm, we have demonstrated recently in a large number of articles [68,67,69,70,55,71,-75,63]. Recognizing also a 4 Dimemsion Space/Time Matrix, wherein there are 2 SD and 2 TD, which provides a simultaneous Information, due to entanglement phenomena, not ruled by the old deterministic, classic physics, but by post-quantum physics evolution (entanglement and disentanglement) we are able to understand why the first phase of hormone action is simultaneous with very beginning of whatever stimulation (for instance, intense digital pressure upon radius or vertebra bone is simultaneous to pancreas size increasing as response to endogenous endocalcin [67, 72, 74, 75]. The second phase, different in nature, is brought about by the contact of ostecalcin with relate receptors on beta-cell outer membrane in Langherans's islets.

Briefly, in health, “intense” digital pressure applied on lumbar or caudal vertebrae (= spinal process), does not cause simultaneously size changes of the stomach, showing that there is not osteoporotic constitution.

On the contrary, in case of osteoporotic constitution, as well as obviously in all stages of ospeoporosis, even in very initial stage, the above illustrated manoeuvre provokes Gastric Aspecific Reflex, whose intensity parallels the seriousness of underlying bone metabolism impairment.

**Current & Future Developments**

The Mediterranean diet is a modern nutritional model inspired by the traditional dietary patterns of some of the countries of the Mediterranean basin, particularly Italy, Greece, Cyprus, Portugal, Turkey and Spain. A main factor in the appeal of the Mediterranean Diet is its rich, full flavoured foods. Margarine and other unhealthy hydrogenated oils (Saturated fat is fat that consists of triglycerides containing only saturated fatty acids) must be avoided, preferring the use of mono-unsaturated olive oil. Red wine is also consumed regularly but in moderate quantities. Regular physical exercise is advisable to enjoy the benefits of the Mediterranian diet. Regular and moderate exercise is generally recommended to help people stay in shape as well as reducing the risks of heart attack, stroke, diabetes and osteoporosis.

Many years of research carried out into the Mediterranean diet and lifestyles show this way of healthy eating and living has many benefits. For example, decreased risk of many chronic diseases such as coronary heart disease, prostrate and breast cancers, osteoporosis and diabetes, obviously in individuals involved by related inherited real risks. Further we have to take into great consideration weight loss, ameliorating both lever and arterial PPARs function, and increasing Adiponectin synthesis, improving cholesterol and blood pressure levels as well as bone microcirculation.

We may solve controversies as about the suggestion to reduce the input of dairy products, which many consider necessary to prevent osteoporosis, by means of personalized diet, prescribed on the base of quantum-biophysical-semeiotic data.

My long clinical experience and researches, referred above, suggest to take into high consideration sea fish, which are rich in Omega 3 fatty acids, I demonstrated efficacious in both increasing mitochondrial Co Q10 synthesis and Co Q10 cycle. Interestingly, such as diet is also based mostly on preventing heart disease, cancer and other CAEM-dependent diseases.

To summarize, I suggest that modified Mediterranean Diet comprehending a high consumption of fruit and vegetables, bread and other cereals, olive oil and fish, making them low in saturated fat and high in monounsaturated fat and dietary fibres, could be worldwide utilize in the future. Finally, the importance of the paramount role of substances, like Co Q10 and Melatonin (I prescribe Coniugated-Melatonin), in osteoporosis primary prevention has been emphasized in this report.

Nowadays, we are able to perform a new efficacious Primary Prevention of osteoporosis, thanks to Quantum Biophysical Semeiotics, on very large scale in individuals, involved by Osteoporosis Biophysical-Semeiotic Constitution “and” inherited osteoporotic real risk, which have to undergo the above-mentioned treatment, rationally prescribed, and bedside monitored. Zimmer *et al*. also

detail discussed the diagnosis, treatment, prevention in the patented work in US20087407753 (**2008**) [76].

## Quantum Biophysical Semiotics of bone lesions

In health, the mean-intense digital pressure, applied directly on a biological system, or, far more frequently exercised indirectly through the stimulation of related trigger points, causes the middle ureteral reflex, typical of Endo-arterial Blocking Device - EDB, Type II, physiological and ubiquitous.
The “intense” compression in the lower third of the radius and of ulna, between the thumb and other fingers of the hand, actives the microcirculation simultaneously, depending on the type I, associated, both locally and throughout the remainder of the skeletal system, for example, in various bones of the skull and lumbar vertebrae, explained by quantum entanglement.
In healthy, digital pressure of "light" intensity exerted on a bone, causes the oscillating upper and lower ureteral reflexes, i.e., vasomotion and vasomotion, which inform the way of being and functioning of local small arteries and arterioles, by Hammersen, or vasomotility, and respectively the nutritional capillaries, or vasomotion, allowing to observe the "simultaneous" intensification of the characteristics fluctuations of ureteral reflex in experimental conditions referred to above.
It follows that the medium-intensity stimulation of a small part of a bone simultaneously provides information on the whole biological system, as is the case for all other tissues.

In fact, in healthy, if the bone stimulation is of medium intensity, after a latency time of exactly 8 seconds, appears the gastric aspecific reflex whose duration is less than 4 seconds, expression of the effectiveness of Microcirculatory Functional Reserve, a great diagnostic significance parametric value, which disappears for the duration of> 3 sec. <4 sec., corresponding to the fractal dimension of the micro-vascular chaotic deterministic dynamics.
The triad of information has led Paolo Manzelli to a wider general reflection on the new "quantum-biophysics," based on the formation of entanglement between quantum particles, electrons and atoms in a "sharing" system of space-time, which produces simultaneous communication of pure information between systems.
However, for this to happen in biological systems must have a sufficient energy level, unavoidable condition for the realization of non-local reality, which provides the normal mitochondrial respiratory activity.
In the presence of an mitochondrial alteration, even if functional one, as is the Congenital Acidosic Enzyme-Metabolic Histangiopathy, out-of oxidative phosphorylation in these intracellular organelles, the non-local reality becomes just local reality with local increase in EM (pyruvic acid converted to lactic acid) and reduction of energy-information, represented by ATP.

### Raggi’s Sign

In healthy, "intense" stimulation of the bone – the pressure above the lower third of the radius and ulna has got a very practical use - shown above, is not accompanied "simultaneously" by the gastric aspecific reflex. (Fig. 1).

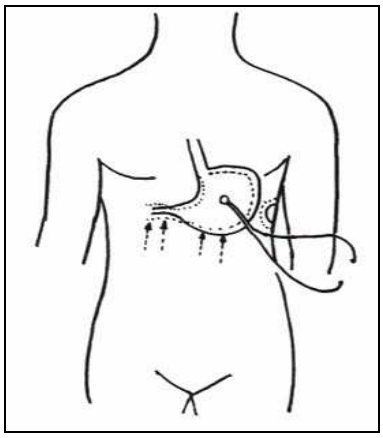


Figure 1
*Gastric aspecific reflex*

In contrast, in the presence of a bone lesion, whatever its nature, inflammation, fibrosis, rheumatic, vascular, neoplastic, etc.. "Simultaneously" to the stimulation is observed the gastric aspecific reflex, whose intensity correlates with the severity of the underlying pathology: a positive Raggi's Sign.
Interestingly, in the presence of bone cancer, primary or metastatic, the reflection is immediately followed by the typical tonic Gastric Contraction.
At this point, having established the bone pain, the physician should proceed with the investigation of the bone location, diagnosing the exact nature, based on the number of signs provided by the Quantum Biophysical Semiotics.
The following experimental evidence supports the above said, in healthy, Raggi's Sign is negative. However, if it exerts intense pressure on any point of the bone system - excluding the articular component, useful but for the provocation of rheumatic-gastric reflex - continued for at least thirty seconds, so as to induce pain in underlying tissue with release of cytokines and significant changes in the local micro-circulatory blood flow, the **Raggi's Sign** becomes transiently **positive**, without being followed by the Tonic Gastric Contraction of course, characteristic of cancers and rheumatic diseases, in case of involvement of sinovium.

Since 2007, Quantum Biophysical Semeiotics was greatly enhanced and made more effective by the contribution afforded by quantum physics, both in terms of clinical research, and on that of the daily practical application, so that the boundaries of his domain had a great expansion. .
It is well known, for example, that so far the clinical diagnosis of **bone metastases** or **perivascular epithelioid cell tumor** (PEComa) was impossible for anyone.
In fact, it is very difficult clinical diagnosis, made out on the basis of reports of symptomatology for imaging, from laboratory and histology test.
Notoriously, the traditional physical semeiotics and symptomatology does not allow the medical finding of bone injuries of any kind, such as bone cysts, and tumors, malignant or benign, out of the arteries not palpable, i.e., localization in internal tissues.
It has recently been reported in world literature that PEComa show an increasing incidence in a variety of anatomical locations. The locations of these lesions are often more widely the uterus and the retro-peritoneum. These tumors are part of a large family that includes, among others,

angiomyolipomas, and the linfangiomiomatosi miomelanociti clear cell tumors of the falciform ligament, also known as PEComa-NOS. There are about fifty known cases of these cancers.
However, based on personal experience with the Quantum Biophysical Semiotics, I am authorized to state that in the future can be detected for much more numerous cases on the condition that doctors around the world will be able to use the original semiotics, which allows faster the generic diagnosis of malignant vascular tumor, whose precise diagnosis will be made in a timely manner in subjects rationally selected on the basis of several clinical signs of malignancy.
As for the easiest method to use, just remember that "mean to moderate" digital pressure, applied directly over a bone, for example, the radio, allows to learn the way of being of the stimulated bone segment through the numerous signs and QBS maneuvers known to readers as: gastric aspecific reflex, followed by tonic Gastric Contraction, complete SIRSI, Domenichini Sign with duration of 4.5 sec. (Glossary), an increase of Acute Phase Proteins, Acute antibody synthesis, local microcirculatory activation type II, dissociated, etc.
On the contrary, if the stimulation exerted on any bone segment is "intense", it causes microcirculatory activation associated, type I, in bones, EV (ATP) increases and thus an higher EI, pure and catalytic energy: the reality in the biological system is both local and non-local one.
For the phenomenon of resonance, a possible bone lesion at a distance is "simultaneously" stimulated, producing a number of reflections (gastric aspecific reflex followed by tonic Gastric Contraction just in case there is cancer), depending on the nature of the disease itself.
**Raggi's Sign** is based on this scientific knowledge, subject of this article, which allows to exclude just in one second the presence of metastases.

## References


[1] Lawrence G. Raisz. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. *Clin. Invest.* 2005. 115:3318-3325 doi:10.1172/JCI27071. http://www.jci.org/cgi/content/full/115/12/3318
[2] Cheung Angela M., Denice S. Feig, Moira Kapral, Natalia Diaz-Granados and Sylvie Dodin and The Canadian Task Force on Preventive Health Care. Prevention of osteoporosis and osteoporotic fractures in postmenopausal women: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ. 2004; 25(11): 170. doi:10.1503/cmaj.1030757. http://www.cmaj.ca/cgi/content/full/170/11/1665
[3] Stagnaro S, Stagnaro-Neri M, Le Costituzioni Semeiotico- Biofisiche.Strumento clinico fondamentale per la prevenzione primaria e la definizione della Single Patient Based Medicine. Ediz. Travel Factory, Roma, 2004. http://www.travelfactory.it/semeiotica_biofisica.htm
[4] Stagnaro-Neri M., Stagnaro S. Introduzione alla Semeiotica Biofisica. Il Terreno Oncologico. Travel Factory, Roma, 2004. http://www.travelfactory.it/semeiotica_biofisica.htm
[5] Stagnaro S, Stagnaro-Neri M, La Melatonina nella Terapia del Terreno Oncologico e del "Reale Rischio" Oncologico. Travel Factory, Roma, 2004. http://www.travelfactory.it/
[6] Stagnaro S, Stagnaro-Neri M, Single Patient Based Medicine.La Medicina Basata sul Singolo Paziente: Nuove Indicazioni della Melatonina. Travel Factory, Roma, 2005. http://www.travelfactory.it/libro_singlepatientbased.htm
[7] Stagnaro-Neri M, Stagnaro S. Diagnosi Clinica Precoce dell'Osteoporosi con la Percussione Ascoltata. ClinTer 1991; 137: 21 -27 [**Medline**]
[8] Stagnaro S. Pivotal role of Biophysical Semeiotic Constitutions in Primary Prevention. Cardiovascular Diabetology, 2003; 2:1.
http://www.cardiab.com/content/2/1/13/comments#5753
[9] Stagnaro Sergio. Biophysical Semeiotic Constitutions, Genomics, and Cardio-Vascular Diseases. *BMC* Cardiovascular Disorders. 2004; http://www.biomedcentral.com/1471-2261/4/20/comments#95454

[10] Stagnaro Sergio. Bedside diagnosing diabetic and dyslipidaemic constitutions and diabetes real risk. 2 October2006 http://www.cmaj.ca/cgi/eletters/175/7/733 2006
[11] Stagnaro Sergio. Hypertensive Constitution accounts for the exsistence of diabetics with and without Hypertension. *Cardiovascular Diabetology* 2006, 5:19 doi:10.1186/1475-2840-5-19.
[12] Stagnaro Sergio. Hypertensive Constitution accounts for the exsistence of diabetics with and without Hypertension. Cardiovascular Diabetology 2006; 5:19 doi:10.1186/1475-2840-5-19.
[13] Stagnaro Sergio. Biophysical-Semeiotic Diabetic and Dyslipidaemic Constitutions and Primary Prevention. Annals of Family Medicine, *2006;* http://www.annfammed.org/cgi/eletters/4/5/427
[14] Stagnaro Sergio. Rimodellamento Microvascolare, Costituzioni Semeiotico-Biofisiche e Reale Rischio Semeiotico-Biofisico. Ruolo dei Dispositivi Endoarteriolari di Blocco neoformati-patologici, www.clicmedicina.it, 2007; 10/4/, http://www.clicmedicina.it/pagine%20n%2028/rimodellamento.htm 2007
[15] Stagnaro Sergio. Bedside diagnosis of osteoporotic constitution, real risk of inheriting ostoporosis, and finally osteoporosis. *Theoretical Biology and Medical Modelling*, 2007; 21 June. http://www.tbiomed.com/content/4/1/23/comments#285569
[16] Stagnaro Sergio. Biological System Functional Modification parallels Gene Mutation. www.Nature.com, March 13, 2008; http://blogs.nature.com/nm/spoonful/2008/03/gout_gene.html
[17] Stagnaro S., Stagnaro-Neri M., Il test della Apnea nella Valutazione della Microcircolazione cerebrale in Cefalalgici. Atti, Congr. Naz. Soc. Ita. Microangiologia e Microcircolazione. A cura di C. Allegra. Pg. 457, Roma 10-13 Settembre 1987. Monduzzi Ed. Bologna, 1987.
[18] Stagnaro S., Stagnaro-Neri M., Una patologia mitocondriale ignorata: la Istangiopatia Congenita Acidosica Enzimo-Metabolica. Gazz. Med. It Arch Sci Med 1990; 149, 67.
[19] Stagnaro S., Stagnaro-Neri M., Una patologia mitocondriale ignorata: la Istangiopatia Congenita Acidosica Enzimo-Metabolica. Gazz. Med. It. – Arch. Sci. Med 1990; 149: 67.
**[20] Stagnaro S.,** Istangiopatia Congenita Acidosica Enzimo-Metabolica condizione necessaria non sufficiente della oncogenesi. XI Congr. Naz. Soc. It. di Microangiologia e Microcircolaz. Abstracts, pg 38, 28 Settembre-1 Ottobre, Bellagio, 1983.
[21] Stagnaro S., Valutazione percusso-ascoltatoria della microcircolazione cerebrale globale e regionale. Atti, XII Congr. Naz. Soc. It. di Microangiologia e Microcircolazione. 1986;13-15 Ottobre, Salerno, e Acta Medit. 145, 163-169.
[22] Stagnaro-Neri M., Moscatelli G., Biophysical Semeiotics: deterministic Chaos and biological Systems. Gazz. Med. It. Arch. Sc. Med. 1996; 155, 125-130.
[23] Stagnaro-Neri M., Stagnaro S., Auscultatory Percussion Evaluation of Arterio-venous Anastomoses Dysfunction in early Arteriosclerosis. Acta Med. Medit. 1989; 5, 141-144.
[24] Stagnaro-Neri M., Stagnaro S. Indagine clinica percusso-ascoltatoria delle unità microvascolotessutali della plica ungueale. Acta Med Medit1988; 4, 91-96.
[25] Stagnaro Sergio. Teoria Patogenetica Unificata, 2006; Ed. Travel Factory, Roma.
[26] Stagnaro Sergio. Epidemiological evidence for the non-random clustering of the components of the metabolic syndrome: multicentre study of the Mediterranean Group for the Study of Diabetes. Eur J Clin Nutr 2007; 7 (65): 66-67 **[Medline].**
[27] Stagnaro-Neri M., Stagnaro S., Stadio pre-ipertensivo e monitoraggio terapeutico della ipertensione arteriosa. Omnia Medica Therapeutica. Archivio, 1989-90; 1-13.
[28] Stagnaro S., West PJ., Hu FB., Manson JE., Willett WC. Diet and Risk of Type 2 Diabetes. N Engl J Med 2002; 24;346(4): 297-298. [**Medline**].
29. Stagnaro S. Role of coronary endoarterial blocking devices in myocardial preconditioning - c007i. Lecture, V Virtual International Congress of Cardiology. 2007; http://www.fac.org.ar/qcvc/llave/c007i/stagnaros.php
[29] Poliquin S, Murray TM, Blondeau L, *et al*. Estimation of the prevalence of low bone density in Canadian women and men using a population-specific DXA reference standard: The Canadian Multicentre Osteoporosis Study (CaMOS). Osteoporos Int 2000;11: 897-904.

[30] Melton LJ, Chrischilles EA, Cooper C, Lane AW, Riggs BL. Perspective: how many women have osteoporosis. J Bone Miner Res 1992;7: 1005-10.
[31] Wathen CN, Feig DS, Feightner JW, Abramson BL, Cheung AM, Canadian Task Force on Preventive Health Care. Hormone replacement therapy for the primary prevention of chronic diseases: recommendation statement from the Canadian Task Force on Preventive Health Care. CMAJ 2004;170(10): 1535-7.
[32] US Preventive Services Task Force. Screening for osteoporosis in postmenopausal women. Ann Intern Med 2002;137: 526-8.

[33] Khan AA, Brown JP, Kendler DL, Leslie WD, Lentle BC, Lewiecki EM, *et al*. The 2002 Canadian bone densitometry recommendations: take-home messages. CMAJ 2002;167(10): 1141-5.
[34] Society of Obstetricians and Gynaecologists of Canada. The Canadian Consensus Conference on Menopause and Osteoporosis, 2002 update [SOGC guideline no 108]. Ottawa: The Society; 2002. http://sogc.medical.org/SOGCnet /sogc_docs/common/guide/pdfs/osteo
[35] Stagnaro-Neri M, Stagnaro S, Acidi grassi Ω-3, scavengers dei radicali liberi e attivatori del ciclo Q della sintesi del CoQ10. Gazz Med It Arch Sc Med 1992; 151: 341-45.
[36] Lenaz G, Parenti Castelli G. Multiple roles of ubiquinone in mammalians cells. Drugs Exptl. Clin Res 1984;10: 481-85.

[37] Lubich T, Bargossi AM, Fiorella PL, *et al*. Metabolic effects of coenzyme Q treatment in high level athletes. VI Simposio Internazionale su: Biomedical and clinical aspects of coenzyme Q. Chairmen: Folkers K, Littarru GP, Yamagamy Y, 22-24 gennaio 1990, Roma. Abstracts, 70.
[38] Stagnaro S, Stagnaro-Neri M. Carenza di CoQ10 secondaria a terapia ipolipidemizzante diagnosticata con la percussione ascoltata. Settimana Italiana di Dietologia. Merano 9-13 aprile 1990. Com.. Abstract. 105 e Epatol. 1991; 37: 17-22.
[39] Stagnaro-Neri M, Stagnaro S. Auscultatory Percussion Coenzyme Q deficiency Syndrome. VI Simposio Internazionale su: Biomedical and clinical aspects of coenzyme Q. Chairmen: Folkers K, Littarru GP, Yamagamy Y, 22-24 gennaio 1990, Roma. Abstracts, 104.
[40] Stagnaro S. Ipercolesterolemia e Coenzima Q10. The Pract Ed It 1990; 133: 5-6.
[41] Stagnaro-Neri M., Stagnaro S, Sindrome clinica percusso-ascoltatoria da carenza di Co Q10. Medic. Geriatr. 1993; XXIV, 239-51.
[42] Baker SK, Tarnopolsky MA. Statin myopathies: Pathophysiologic and clinical perspectives. Clin Invest Med 2001; 24: 2258-2272.
[43] Leung NM, Ooi TC: Use of statins and fibrates in hyperlipidemic patients with neuromuscular disorders. Ann Intern Med 2000; 132:418-419.
[44] Mitchel P. The vital protonmotive role of Coenzyme Q. VI Simposio Internazionale su: Biomedical and clinical aspects of coenzyme Q. Chairmen: Folkers K., Littarru G.P., Yamagamy Y., 22-24 gennaio 1990, Roma. Abstracts, 77.
[45] Trichopoulou A., *et al*. Modified Mediterranean diet and survival: EPIC-elderly prospective cohort study. BMJ 2005;330:991 (30 April), doi:10.1136/bmj.38415.644155.8F (published 8 April 2005).
[46] Huijbregts P, Feskens E, Rasanen L, Fidanza F, Nissinen A, Menotti A, et al. Dietary pattern and 20 year mortality in elderly men in Finland, Italy, and the Netherlands: longitudinal cohort study. BMJ 1997;315: 13-7.
[47] World Cancer Research Fund and American Institute for Cancer Research. Food, nutrition and the prevention of cancer: A global perspective. Washington DC: WCRF and AICR, 1997.

[48] Knoops KT, de Groot LC, Kromhout D, *et al*. Mediterranean diet, lifestyle factors, and 10-year mortality in elderly European men and women: The HALE project. JAMA 2004; 292: 1433-9.
[49] Bouillon; R.: US20080032955A1 (**2008**).
[50] Patell V.M.: WO2008004026 (**2008**).
[51] Dillaha L., Adams, B.: WO2008057738 (**2008**).

[52] Stagnaro Sergio. Reale Rischio Semeiotico Biofisico. I Dispositivi Endoarteriolari di Blocco neoformati, patologici, tipo I, sottotipo a) oncologico, e b) aspecifico. Ediz. Travel Factory, www.travelfactory.it, Roma, Luglio 2009.
[53] Stagnaro Sergio Endothelial cell function can ameliorate under safer drugs, such as Melatonin-Adenosine. BMC *Cardiovascular disorders*. 2004; http://www.biomedcentral.com/1471-2261/4/4/comments.
[54] Davis PF., Barbee KA. *et al*. Hemodynamics and Atherogenesis. Endothelial Surface Dynamics in Flow Signal Transuction. Recent Advances in Atherosclerosi Research. Annals of the New York Acadèmy of Science. 1995; Vol 748., 86-103.
[55] Stagnaro Sergio. Diagnosi clinica di cuore sano in un secondo! www.fce.it . 2008; 7 Aprile. http://www.fcenews.it/index.php?option=com_content&task=view&id=1218&Itemid=47
[56] Ladizesky MG, Boggio V, Cutrera RA, *et al*. Melatonin effect on bone metabolism in rats treated with methylprednisolone. Journal of Pineal Research, 2006; 40(4): 297-304.
[57] Ostrowska Z, Kos-Kudla B, Nowak M, *et al*. The relationship between bone metabolism, melatonin and other hormones in sham-operated and pinealectomized rats. Endocrine Regulations 2003; 37: 211–224.
[58] Ladizesky Marta G, Boggio Verónica, Albornoz L., et al. Melatonin increases oestradiol-induced bone formation in ovariectomized rats. Journal of pineal research, 2003; 34(2): 143-151.
[59] Kesemenli CS . Necmioğlu. The role of melatonin as a link between head injury and enhanced osteogenesis . Medical Hypotheses 2003; 65(3): 605 - 606.
[60] Steinhilber D, Brungs M, Werz O, *et al*. The Nuclear Receptor for Melatonin Represses 5-Lipoxygenase Gene Expression in Human B Lymphocytes. Experimental Biology and Medicine1995; 270(13): 7037-7040.
[61] Olsen, B., Ueki, Y.: WO2008048466 (**2008**).
[62] Ke, H.Z., Thompson, D.: EP1932543 (**2008**).
[63] Tamura T, Yoneda M, Yamane K, *et al*. Serum leptin and adiponectin are positively associated with bone mineral density at the distal radius in patients with type 2 diabetes mellitus . Metabolism, 2003; 56(5): 623 – 628.
[64] Zoico E, Zamboni M, Di Francesco V, *et al*.
Relation between adiponectin and bone mineral density in elderly post-menopausal women: role of body composition, leptin, insulin resistance, and dehydroepiandrosterone sulfate. J Endocrinol Invest. 2008; 31(4): 297-302.
[65] Shinod Y, Yamaguchi M, Ogata N, *et al*. Regulation of bone formation by adiponectin through autocrine/paracrine and endocrine pathways. Journal of Cellular Biochemistry. 2008; Volume 99 Issue 1, Pages 196 – 208.
[66] Stagnaro S, Paolo M. www.ilpungolo.com. 2008; 03 Gennaio. Limiti della Medicina Ufficiale. L'Esperimento di Lory. http://www.ilpungolo.com/leggi-tutto.asp?IDS=13&NWS=NWS5267.
[67] Stagnaro S, Paolo M. L'Esperimento di Lory. Scienza e Conoscenza, 2008; N° 23, 13 Marzo. http://www.scienzaeconoscenza.it//articolo.php?id=17775
[68] Stagnaro Sergio. Il test Semeiotico-Biofisico della Osteocalcina nella prevenzione primaria del diabete mellito. www.fce.it . 2008: Febbraio http://www.fcenews.it/index.php?option=com_content&task=view&id=909&Itemid=47
[69] Stagnaro Sergio. Reale Rischio Congenito di Cancro Renale Diagnosticato con la Semeiotica Biofisica: il Segno di Pollio. www.ilpungolo.com, 2008; 25 Marzo, http://www.ilpungolo.com/leggi-tutto.asp?NWS=NWS5480&IDS=13
[70] Stagnaro Sergio. Melanoma? Escluso in 1 Secondo con La Semeiotica Biofisica Quantistica. Il Reale Rischio Congenito di Melanoma. www.ilpungolo.com, 2008; 9 Aprile, http://www.ilpungolo.com/leggi-tutto.asp?IDS=13&NWS=NWS5524
[71] Stagnaro Sergio. Non Local Realm. Response to Selection for Social Signalling Drives the Evolution of Chameleon Colour Change. 2008; 01 February. www.plos.com,

[72] Stagnaro Sergio e Manzelli Paolo. Semeiotica Biofisica Quantistica: Livello di Energia libera tessutale e Realtà non locale nei Sistemi biologici. www.fce.it, 2008; 29 maggio, http://www.fcenews.it/index.php?option=com_content&task=view&id=1421&Itemid=47
[73] Stagnaro Sergio. Bedside Diagnosing Pheochromocytoma, since its initial stage of Inherited Real Risk. *Cases Journal* 2008, http://www.casesjournal.com/content/1/1/30/comments#304598
[74] Stagnaro Sergio. Semeiotica Biofisica Quantistica: Diagnosi Clinica di Melanoma a partire dal suo Reale Rischio Congenito. www.fce.it, 23 luglio 2008, http://www.fcenews.it/index.php?option=com_content&task=view&id=1599&Itemid=45
[75] Stagnaro Sergio. Il Cammino della Medicina : Semeiotica Biofisica Quantistica. Mutazioni Genetiche E Disfunzioni Dei Sistemi Biologici. www.ilpungolo.com, 30 Aprile 2008, http://www.ilpungolo.com/leggi-tutto.asp?NWS=NWS5548&IDS=1369.
[76] Zimmer, A., Karsak, M., De Vernejoul, M.-C., Bab, I., Shohami, E., Mechoulam, R.: US2008 7407753 (**2008**).
[77] Stagnaro Sergio e Caramel Simone (2011) The Principle of Recursive Genome Function: QBS clinical and experimental evidences, Journal of Quantum Biophysical Semeiotics, 2011 http://www.sisbq.org/uploads/5/6/8/7/5687930/prgf_qbsevidences.pdf
[78] Stagnaro Sergio. Rinaldi's Sign, Journal of Quantum Biophysical Semeiotics, 2011 http://www.sisbq.org/uploads/5/6/8/7/5687930/raggi_sign_english.pdf