Primary Prevention of T2DM and Inherited Real Risk of Type 2 Diabetes Mellitus

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ABSTRACT

Mit-DNA is mainly responsible for cell respiration in biological systems, and the genetic alteration of mit-DNA affects mitochondrial activity. It will be here analyzed a well defined mitochondrial cytopathy which is connected, from the moment of birth, with several inherited diseases, such as diabetes. The chance to investigate, indirectly and through bed-side evaluation, mitochondria functionality opens new ways to understand and face the very beginning states of type 2 diabetes mellitus, even silent and not yet clinically diagnosed, and of the 'Inherited Real Risk' of diabetes, giving original impulses to diagnosis and prevention. Finally, a multidisciplinary and integrated approach involving biology, physics, mathematics, chemistry, philosophy, etc. opens new perspectives both for classical and social sciences.

Introduction

This paper highlights the central role of mitochondria and mitochondrial DNA (mit-DNA) in the process that underlies the metabolic disorders and microcirculatory alterations, pre-pathological conditions of type 2 diabetes mellitus. For this purpose it is useful the Quantum Biophysics Semeiotics - QBS, extension of the classical semiotics with the support of quantum and complexity theories, a scientific approach first described by Stagnaro et al. (Manzelli, 2007b) based on the Congenital Acidosic Enzymo-Metabolic Histangiopathy – CAEMH (Stagnaro, 1985), a unique mitochondrial cytopathy, present at birth and subject to medical therapy.

We will see how chaos theory, quantum theory, and concepts such as synchronicity, entanglement, strange attractors, non-local reality, energy-information and DNA "antenna" defined by Manzelli (2007), are crucial for understanding the diagnosis, prevention and therapy of Type 2 Diabetes Mellitus – T2DM, and especially to reveal the Inherited Real Risk of diabetes (Stagnaro, 2009a).

The autopoietic theory (Varela, 1974) will be a useful key-tool to interpret the behavior of biological systems here analyzed.

According to the research of Stagnaro, today the doctors should be able to evaluate, at the bedside of their patients, simply using the stethoscope (Stagnaro, 1978),

mitochondria functionality, as well as the functionality of all biological systems. It is now possible, from the moment of birth, to make a diagnosis in order to detect the presence of Inherited Real Risk of T2DM linked with 'Diabetics and Dyslipidemic Constitution' (Stagnaro, 2009), so that an intelligent prevention strategy can be implemented only on those subjects with Real Risk, without incurring additional costs for the NHS[1]. The prevention done on the basis of QBS constitutions - i.e. Coronary Artery Disease – CAD (Caramel, 2010a), Oncological Terrain (Caramel, 2010b), Diabetics Constitution (Stagnaro, 2009), etc. - will prevent the onset of the more serious diseases that humans suffer from today - for example, cancer, diabetes, ischemic heart diseases, including myocardial infarction.

1. State of the art

Type 2 Diabetes Mellitus

Diabetes mellitus, often simply referred to as diabetes, is a condition in which a person has high blood sugar, either because the body does not produce enough insulin[2], or because cells do not respond to the insulin that is produced. There are three main types of diabetes:

- Type 1 diabetes – T1DM: results from the pancreatic islet β-cell, failure to produce insulin, and presently requires the person to inject insulin.
- Type 2 diabetes – T2DM: results from insulin resistance, a condition in which cells fail to use insulin properly, sometimes combined with an absolute insulin deficiency.
- Gestational diabetes: is when pregnant women, who have never had diabetes before, have a high blood glucose level during pregnancy. It may precede development of T2DM.

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of gluco-corticoids, and several forms of monogenic diabetes. Both type 1 and 2 are chronic conditions that usually cannot be cured. Serious long-term complications include cardiovascular disease, chronic renal failure, retinal damage, exclusively in patients involved by related inherited real risks, as we will see later in this paper (Stagnaro, 2009). Adequate treatment of diabetes is thus important, as well as blood pressure control and lifestyle factors such as smoking cessation and maintaining a healthy body weight.

As of 2000 at least 171 million people worldwide suffer from diabetes, or 2.8% of the population. T2DM is by far the most common, affecting 90 to 95% of the World diabetes population. T2DM is one of the most common human diseases, particularly in high developed countries, from the socio-economic view-point, shows a persistent and worrying annual incidence. For instance, although official data are lacking, in Italy there are 2-3 millions of diabetics, with yearly increasing of 6%, including all diabetic types, really different from both aetiopathogenetic and clinical point of view.

In fact, DM represents a *syndrome*, metabolic in origin, very complicated in its aetiopathogenesis, surely genetically based, characterized by relative or absolute insulin-deficiency.

T2DM represents a multi factorial and heterogeneous syndrome, which is characterized by insulin action derangement (insulin resistance) which may be combined with insulin secretion impairment (pancreatic β–cells insufficiency). Insulin resistance is defined as a defect in the ability of skeletal muscle to take up glucose in response to insulin (Cheatham, 1995). In fact, skeletal muscle is the major target tissue into which insulin promotes the transport of glucose.

Blood glucose is obviously absorbed also by lever as well as adipose tissue, whose insulin receptors show an abnormal sensitivity to hormone in a highly differentiated manner: lever cell insulin receptors are typically well-functioning in lithyiasic constitution! (Stagnaro, 2009). This action of insulin is regulated by genetic factors, environmental factors, blood-flow, circulating substances, and insulin signalling pathways (Hsueh, 1997).

Notoriously, a large number of diseases are associated with hyperinsulinemia-insulin resistance - IIR, such as obesity, particularly the visceral type, where one observes a direct link between insulin resistance, non insulin-dependent diabetes mellitus (NIDDM or T2DM), dyslipidemia, and arterial hypertension (Stagnaro, 1990).

In addition, numerous substances from fat tissue appear to suppress insulin-mediated glucose up-take, including free fatty acids, tumour necrosis factor-alpha (TNF-α) and possibly leptins (Haffner, 1997). Infusion of these factors into normal animals suppresses insulin-mediated glucose up-take (Hotamisligil 1995, Kiesselbach 1988).

According with the work of Stagnaro (2004c), insulin resistance and insulin-secretion derangement are correlated in a stable manner and both play a pivotal role in the onset of T2DM. In fact, e.g., insulin-secretion is physiologically ruled by insulinemia, by means of a feed-back mechanism, through insulin-receptors localized on the membrane of insular β-cell: the two factors are strictly related each other at large number of different levels. Due to these reasons the clinical on-set of T2DM appears later, because insulin-resistance in liver, adipose cells of the abdomen wall and skeletal muscles during the initial stage, i.e., for years or decades, may be balanced by increasing of the insulin secretion.

Opie (1901) described the "hyaline degeneration" of the Langherans pancreatic islets of hyperglycaemic patients, suggesting a possible relation to DM, although in that period amyloid protein was not yet identified as product of insular origin. In 1986, the protein secreted by β-cells was identifies and termed insular polypeptide amyloid (Westermark, 1986).

Amyloid protein is composed by dense, interlacing fibrillae, which are coloured by red and are birefrigent to polarized light. These fibrillae are formed by 20 proteins and a large number of them are considered related to specific diseases. Insular amyloid is present in 90 % of diabetic (NIDDM) patients (Hoeppener, 2000), composed of normal proteins, as component of serum P amyloid, and proteoglycans of heparansulfate type, present in both serum and healthy tissues.

The serum P protein component, related to acute phase proteins, may be associated to all amyloid fibrillae, which therefore are protected against proteolysis.

In addition, experimental evidence shows the importance of this protein in case of amyloidosis "in vivo": in gene *knocked-out* rats the systemic amyloidosis on-set is later and its severity is less intense. Insular amyloidosis is related to the loss of approximately 40 - 50% of β-insular tissue.

Human insular amyloid polypeptides bring about cytotoxity by a large number of pathological mechanisms, producing amyloid fibrillae. In addition, they undergo to glycation process. Hyperglycaemia causes the production of amyloid both increasing the production of insular amyloid polypeptides and augmenting their fibrillopoietic properties (Hoeppener, 2000).

It is generally admitted that the NIDDM may occur at least 12 years before the clinical diagnosis is made, and retinopathy can develop at least 7 years before the diagnosis. During the time that diabetes is undiagnosed and untreated, complications, that could be avoided, are developing. Therefore, early diagnosis should be established to avoid those complications. In fact, in order to prevent well known diabetic complications, it is extremely necessary that the doctors could use a "clinical" tool reliable in diagnosing early diabetes mellitus, i.e., "since its initial stages" (Stagnaro 1986, Stagnaro 1993b). Until now, unfortunately, diabetes mellitus is too often diagnosed accidentally, e.g., by occasional urinary or blood tests. Furthermore, epidemiologic studies indicate that 50% of individuals with 2-hour post glucose challenge values over 200 mg/dL, a value diagnostic for diabetes, were not previously diagnosed as being diabetic (Harris, 1993).

T2DM is now widely considered to be one component within a group of disorders called the metabolic syndrome[3], both classic and "variant", (Stagnaro, 1993b). Such as syndrome, also known formerly as dysmetabolic syndrome X, is formed by some characteristic factors: abdominal obesity, atherogenic dyslipidemia (elevated triglyceride [TG] levels, small low-density lipoprotein [LDL] particles, low high-density lipoprotein cholesterol [HDL-C] levels), elevated blood pressure, insulin resistance (with or without glucose intolerance), and prothrombotic and proinflammatory states.

Genetics, mit-DNA and chaotic dynamics

Several works of the last decades evidence the importance of deterministic chaos and fractals in genetics (Capra, 1997).

By studying the complexity of biological systems, the focus has shifted from the structures to the processes that 'emerge' from them. In the past there was the view of genes as stable and clearly distinct units that transmit hereditary characteristics. Genetic stability is instead an emergent property that stems from the complex dynamics of the whole cellular network.

The stability of genetic structure is the result of a well-orchestrated dynamic process that requires the participation of a large number of enzymes, organized in complex

metabolic networks that regulate and ensure both the stability of DNA molecules, and the accuracy of their duplication. During duplication the cell not only passes the double helix newly replicated DNA but also a complete set of enzymes, coenzymes and ions needed for metabolic processes such as membranes and other cellular structures: in short the entire cell's network. In this way, cellular metabolism can perpetuate itself without ever leaving the pattern of their self-generated networks.

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

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

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

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

of biological development, an embryo may be different from the initial stages - for example in case of individual genes or whole cells are accidentally destroyed - then still reach the same mature form that characterizes the species to which belongs.

Natural selection does not operate on individual genes but on the scheme of self-organization bodies. It is possible to represent the whole process of biological evolution as a trajectory in a phase space that moves within a basin of attraction to an attractor (Medio, 1992) that describes the functioning of the body in the stable form that characterizes his adulthood. Complex systems exhibit nonlinear structural stability. A basin of attraction can be distorted or disturbed without changing the fundamental characteristics of the system. In the case of an embryo during evolution, it means that it is possible to change, to some extent, the initial conditions of the process without seriously damaging the development of the whole organism. Therefore, the stability of development, which remains a mystery from the perspective of genetic determinism, is clearly a consequence of basic properties of complex nonlinear systems.

DNA mutation and recombination are the two main way of bacterial evolution, but Margulis (1993) discovered a third way: the symbiosis. The most remarkable evidence of evolution through symbiosis - the tendency of different organisms to live in close association with each other, as the bacteria in our gut - is offered by mitochondria[4], the power plants that are found within most nucleated cells.

These fundamental components of all animal and plant cells that perform cellular respiration, contain their own genetic material and reproduce independently and at different times than the rest of the cell, and in fact have their own DNA, mitochondrial DNA[5].

Quantum-Deterministic chaos and non-local reality

Deterministic chaos has been defined[6] as the 'stochastic or probabilistic behavior occurring in a deterministic system' and its main characteristics are the uncertainty and unpredictability, but it is possible to detect and investigate it and to get qualitative information through invariant statistic measures such as LCE[7], fractal dimension[8] and entropy[9] (Medio, 1992).

Entropy represents the rate of uncertainty, or equivalently, the rate of variation of qualitative information of dynamical systems, and is important in the causal interpretation of quantum theory (Bohm, 1980), which supposed the electron to be a certain kind of particle which follows a causally determined trajectory[10]. In addition to the Newtonian classical potential, the particle[11] moves according to a new potential, called Quantum Potential – QP – which is determined by the quantum wave field[12], or wave function. QP is independent of the strength, or intensity, of the quantum field but depends only on its form, so that the information in the form[13] of the quantum wave directs the energy of the electron and even distant features of the environment can effect this movement in a deep way.

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

Sub-quantum behaviors and biological systems dynamics are usually considered as separated and different worlds, but there are some interesting works as Lory's experiment (Stagnaro, 2008) that open new perspectives about the presence of non-local reality in biological systems. Furthermore, since life system is based on the communication system, DNA functioning can not only be seen as a storage of genetic information. We can consider DNA/RNA dynamic system as an Information Energy – EI – catalyst (Manzelli, 2009) able to transmit and receive bio-physical quantum signals to and from the proteins in the living cells, so DNA can be thought as an "antenna" transmitting nonlocal information[14] through 'gene quantum signals'.

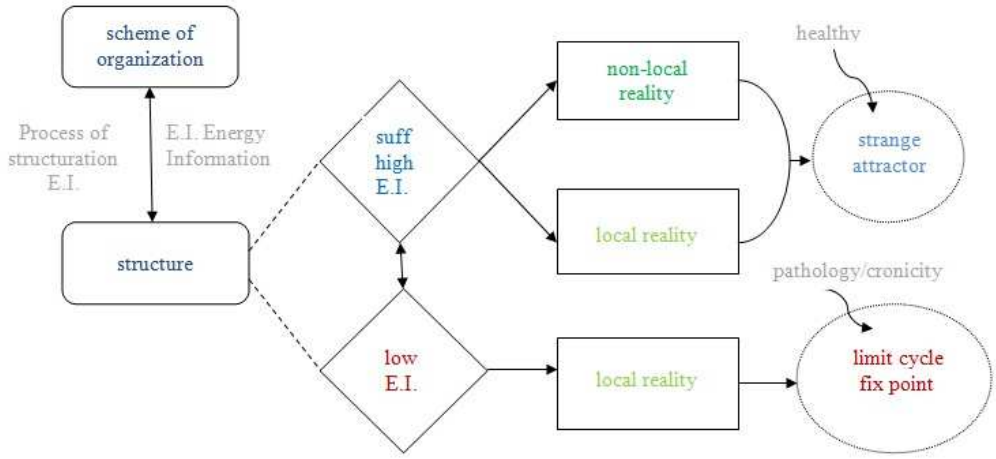
In biology, Varela et al. (1974) proposed the theory of autopoiesis, useful to understand the connection between organization and structures in living systems. An autopoietic system, so as described by Maturana and Varela, is based on a scheme of autopoietic organization through a process of structuring which can lead to different structures. The autopoietic organization is conservative and always acts on itself: self-production, self-regulation, self-referential, recursion, circularity. The scheme of organization works relentlessly to achieve the autopoiesis through a continuous process of structuring, generating dissipative structures with non-linear dynamics (Prigogine, 1967).

There is structural coupling between organization (conservative) and structure (dissipative) to achieve always the autopoiesis. If there was a tendency to disease (or if there is pathology), the organization would always be orientated towards the survival, materializing and engaging compensatory mechanisms to restore groped the simultaneity and synchronicity.

In a previous work (Caramel, 2010b) we tested in biological systems the hypothesis of the correlation between nonlocal reality and deterministic chaos, of the co-presence of local reality and non-local reality in physiological states, and of a sufficient high amount of information energy – EI – as catalytic process to maintain nonlocality in the autopoiesis.

If the system was fully healthy, there would be actually a non-local reality (parallel to the local reality) - simultaneity and synchronicity - and the presence of deterministic chaos (chaotic or strange attractor). If there was disease, the autopoiesis would still be present, but the non-local reality and the correlated strange attractor equlibria, corroborating the presence of deterministic chaos, would disappear so that we would observe just limit cycle equilibria in the case of pathology, and fixed points in case of chronicity (Scheme 1).

Furthermore, chaotic determinism, and quantum determinism as suggested by David Bohm, could merge together in a new philosophical idea of 'quantum-chaotic determinism'[15], corroborated by QBS and Manuel's Story[16], where the 'cause and effect' is replaced just by a potential causality.



Scheme 1. Autopoiesis and Energy Information

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

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

Inherited Real Risk of Type 2 Diabetes Mellitus

According to Stagnaro (2007), genome's information are transmitted simultaneously both to parenchyma and related microvessels, so that mutations in parenchymal cell n-DNA and mit-DNA are the *conditio sine qua non* of the most common human disorders, like diabetes, CAD, and cancer, today's epidemics.

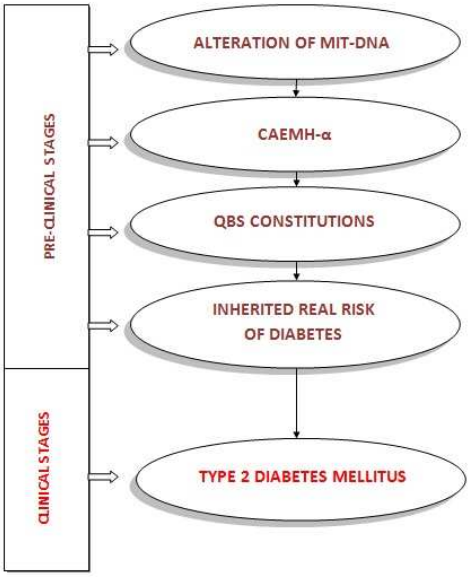
In fact, all these diseases are based on a particular congenital, functional, mitochondrial cytopathy, mostly transmitted through mother, and defined Congenital Acidosic Enzyme-Metabolic Histangiopathy, CAEMH (Caramel, 2010b).

The contribution of these modifications to the relative pattern of diabetic syndrome, based always on genetic or inborn errors – CAEMH - is different from patient

to patient and during the disorder's evolution. For instance, in case of diabetic syndrome, insulin-secretion increases silently for years or decades, before appearing T2DM. This is a pre-clinical stage that is not detectable through usual clinical tests, so it needs to explore new approaches, such as that introduced by Quantum Biophysical Semeiotics – QBS – (Stagnaro, 2007b) which through bed-side evaluation, can assess the existence of pre-metabolic syndrome[17], that can last for years or decades, pre-clinical stage of the disease still potential or on training (evolution to pathology, pre- morbid state or gray area), so allowing an effective prevention (Scheme 2).

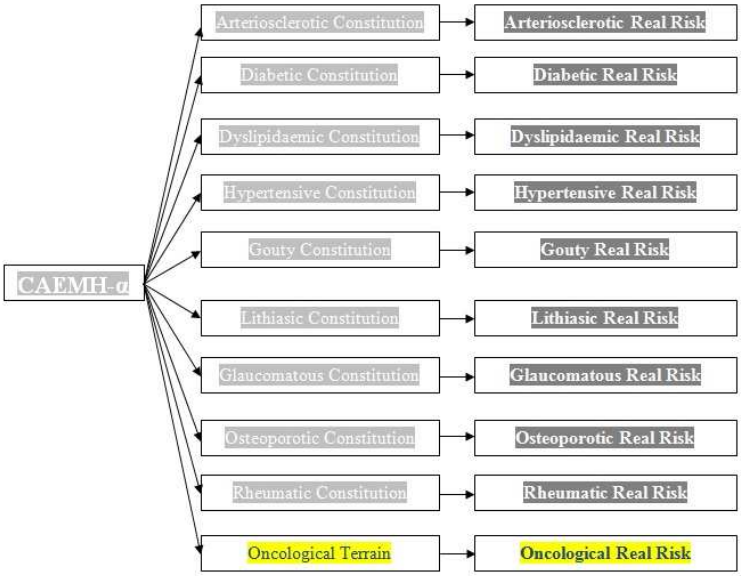
In addition, parenchymal gene mutations cause local microcirculatory remodeling, so doctor can evaluate it at the bedside in a reliable manner, gathering indirect information on inherited modifications of relative parenchymal cell, since biological system functional modifications parallel gene mutation, according to Angiobiopathy theory (Stagnaro, 2004).

The presence of intense CAEMH – termed CAEMH-α - in a well-defined area, i.e., pancreas, involved by gene mutations in both n-DNA and mit-DNA, is the ground for one or more biophysical semeiotics constitutions[18] (Stagnaro, 2004c) which could brings about their respective congenital Real Risks - RR (Scheme 3) characterized by microcirculatory remodeling from biophysical-semeiotic viewpoint, especially intense under environmental risk factors.



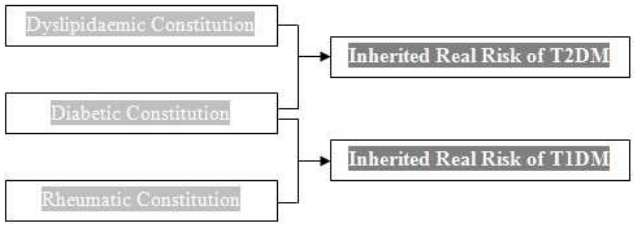
Scheme 2. Pre-clinical and clinical stages of type 2 Diabetes Mellitus

Such as congenital microvascular remodeling, shows since birth interesting structures, i.e., newborn-pathological, type I, subtype b), Endoarteriolar Blocking Devices, EBD, localized in small arteries, according to Hammersen (1968). As a consequence of above, briefly referred remarks, physicians are able nowadays to demonstrate the presence of typical pathological EBD in well defined microvessels, which play a central role in T2DM Inherited Real Risk.



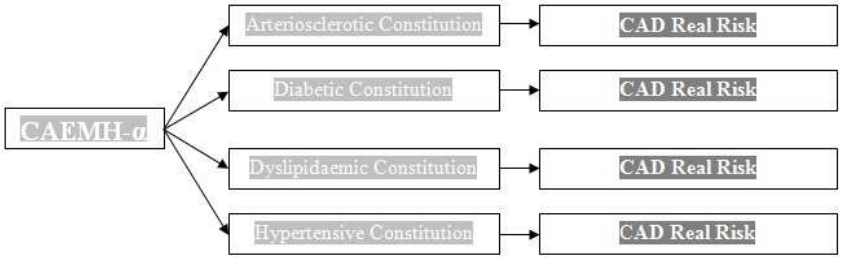
Scheme 3. CAEMH-a, QBS constitutions and associated real risks

Notoriously, T2DM and obesity, major health problems worldwide, are considered to be closely related (Stagnaro, 1993b, Stagnaro, 1997a). In fact, T2DM can involve exclusively individuals with both dyslipidemic and diabetic constitutions (Stagnaro, 2004c), because the accumulation of triglycerides an cholesterol in cells lets less sensitive to the hormone the local insulin receptors of muscle cells, but also those of adipose tissue, especially visceral. Therefore, there is an increased insulin production in pancreatic islets, which functionally collapse to T2DM, after a period of insulin hypersecretion, in the case of inherited real risk of diabetes depending on diabetics constitution. If there is just diabetics constitution, but associated with autoimmune rheumatic constitution, there may happen only T1DM (Scheme 4).



Scheme 4. Diabetic constitution and inherited real risks

Furthermore, diabetic and dyslipidaemic constitutions could be responsible of Coronary Artery Disease – CAD inherited real risk (Caramel, 2010a), as shown in Scheme 5.



Scheme 5. CAEMH-a, QBS constitutions and inherited real risk of CAD

Nuclear Peroximose Proliferator-Activated Receptors - PPARs (Auwerx, 1999) play a pivotal role in the development of metabolic syndrome, T2DM, and in many cardiovascular disorders is certainly of paramount importance, but according with Stagnaro (1993), we have to consider the existence of both QBS diabetic and dyslipidaemic constitutions, *conditio sine qua non* of both metabolic syndrome (classic and "variant") and the most severe human diseases.

It is now well known that treating metabolic syndrome can prevent or ameliorate cardiovascular disease and T2DM (Knowler, 2002). The metabolic syndrome is a highly prevalent clinical entity, so obesity, PPARs modulation and insulin resistance are the central components of this complex syndrome, and diet and physical exercise can prevent a large number of DM (Pan 1997). However, all these events can occur only in individuals with diabetic as well as dyslipidemic constitutions that represent the first stage in the development of all disorders at the base of metabolic syndrome (Stagnaro, 2002).

As regards the essential fact that the fall in insulin secretion, leading to hyperglycaemia, separates patients with metabolic syndrome in two groups, *with* or *without* overt diabetes, we have to pay attention to the presence of the above-mentioned QBS constitutions, associated or isolated, which enlighten the real reason of the different events. In fact, the fall in insulin secretion can occur exclusively in patients involved by both constitutions.

Patients with IIR are "at real risk" for both CAD (Caramel, 2010a), and a lot of others metabolic disorders, including T2DM, as allows us to state a long clinical and experimental evidence, i.e., acute myocardial infarct at the age of 70 years, occurred in the absolute absence of well-known risk factors, generally admitted by all authors, but on the base of "diabetic, dyslipidemic, hypertensive, Oncological QBS constitutions" and IIR, however, properly controlled by diet, etymologically speaking.

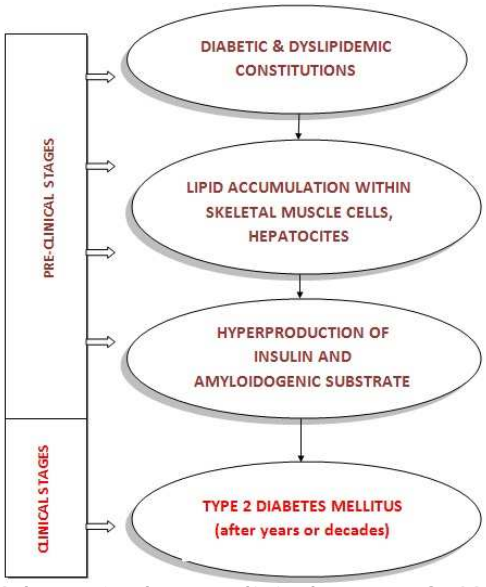
The increased risk is related to the association of diverse factors with hyperinsulinemia-insulin resistance - IIR syndrome (classic and "variant" metabolic syndrome), although IIR for itself can increases the risk for CAD. In fact, four large prospective studies have demonstrated that hyperinsulinemia is an independent risk factor for CAD in Caucasian males; however, similar finding have not been demonstrated in women and have not been addressed in other ethnic groups (Welborn 1979, Wingard 1995).

According with Stagnaro (1990, 1995) clinical researches, we must go "beyond hyperinsulinemia-insulin resistance" to comprehend better the onset of both cardiovascular disease and T2DM, unavoidable condition for a successful primary prevention of a large number of metabolic disorders (Cucimetieri, 1980 Williams 1994). Accurate study of EBD in general, and those of coronary artery in particular, now-a-days possible "at the bed-side" by the aid of QBS, and the different QBS constitutions have opened new and promising ways in primary prevention and in a better comprehension of both arteriosclerosis, including CAD, and T2DM. Stagnaro clinical researches enlighten the intriguing P. Hayden's (1998) theories, and he completely agrees with him: "What is even more interesting is the possibility that T2DM may be a vascular disease with a common genetic abnormality located in the endothelial nitric oxide gene (eNOS) itself, common to both T2DM and Cardiovascular disease" (personal communication).

Furthermore, as regards to the diagnosis of inherited real risk of T2DM, from the moment of birth there is the presence of diabetic constitution, always associated with dyslipidemic constitution, independently of raised lipid blood level in subsequent time.

Later on, through QBS we can observe a second stage, characterized by lipid accumulation within skeletal muscle cell, hepatocites, i.e. classical and "variant" metabolic syndrome, where there is not lipid accumulation in hepatocytes (Schick, 1993), and in pancreatic cells, and local insulin resistance occurs. Under such pathological conditions, the pancreas produces more insulin and the amyloidogenic substrate amylin resulting in islet amyloid formation, according to P. Hayden (2002a, 2002b).

In fact, at this point, from QBS view-point, Langheran's islets interstitium appears clearly increased in size, due to islet amyloid deposit: pancreatic-"in toto" urethral reflex is augmented in a clear-cut way, preceding and accompanying T2DM[19]. Finally, after years or decades, as a consequence of insulin secretion failure, T2DM occurs, according to Scheme 6.



Scheme 6. The pre-clinical stages of T2DM

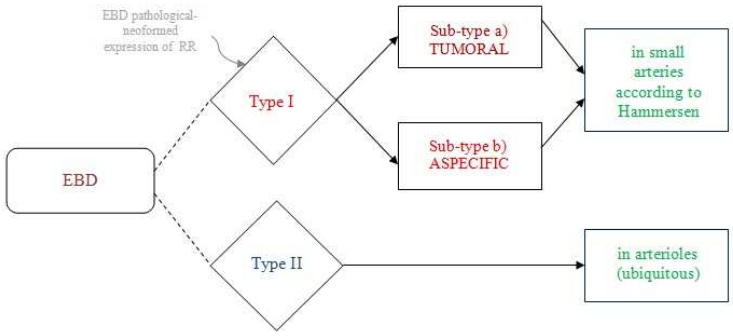
Scheme 6 shows that in case of inherited real risk of diabetes, diabetic constitution is always associated with dyslipidemic constitution, which brings together to a lipid accumulation within skeletal muscle cell, hepatocites (absent in 'variant' form of metabolic syndrome), independently of raised lipid blood level, and later on to hyperproduction of both insulin as well as amyloidogenic substrate of amylin, i.e., metabolic syndrome, classic or 'variant', and only after years or decades to T2DM.

Through the objective QBS examination in a few minutes, it is possible to recognize and quantify if a patient has got any QBS constitution and congenital Real Risk (RR) to have a disease by mean the observation of EBD, type I, subtype a) cancerogenous (Scheme 3, in yellow) b) nonspecific (Scheme 3, in gray, present in all the other more frequent and severe disease).

The EBD is a kind of dam which opening or closing itself regulates blood flow in microvessels directed to the parenchyma (tissue, substance of a body). With a simple stethoscope it is detectable if there is a clear genetic predisposition to have a disease such as

cancer, diabetes or CAD, and it is possible to quantify and monitor it over time since birth. So there is the possibility of implementing a prevention on a huge hall in individuals clinically finally selected in a rational way. This new way of prevention will not allow to materialize physical illness, which can be anyway potentially present (or be RR as "residual") at potential level. As similarity we can think of butterfly valves that regulate the flow and mixture of air and gasoline in car engines, since the EBD are dams that are simply regulating blood flow to the parenchyma[20], precisely cells of various tissues. If these DEB are tough, rigid, inelastic, there is RR.

There are EBD Type I - located in small arteries, according to Hammersen - and Type II – they can be found in the arterioles that are, according to Hammersen, between small arteries and capillaries (Scheme 7): only type II is ubiquitous, in the sense that it is observed everywhere, in all arteries (Scheme 13). Even these physiological types get sick or old. However, the other types, pathological-neoformed, are expressions of the RR, of potential disease, they occlude more, but through therapy they can be transformed from the subtype a) tumoral, to subtype b) aspecific, and then in "physiological" type, decreasing gradually their amount[21].



Scheme 7. Endoarterial Blocking Devices (EBD)

2. QBS diagnosis of T2DM and of its inherited real risk

Microcircular Functional Reserve

Alterations of mit-DNA and n-DNA cause CAEMH in parenchymal area, a parenchymal gene mutation that induces, in case of intense CAEMH-α, a local microcirculatory remodeling (LMR), a congenital microvascular remodeling possible to evaluate and investigate getting information about parenchymal cells through several biophysical semeiotic signs and behavior. For instance, through the observation of EBD and their structure and functioning on pancreatic microvessels we can study the LMR and investigate if there is T2DM or inherited real risk of diabetes and endothelial dysfunctions.

A lowering microcirculatory blood flow induces a LMR due to EBD type 1 subtype b), aspecific, synonymous of reduced tissue oxygenation (Scheme 7). Through QBS we can measure and evaluate the Microcirculatory Functional Reserve (MFR) activity of related

microvessels. MFR is correlated with microcirculatory bed or Tissue Microvascular Unit (T.M.U.) and is possible to evaluate it through the observation of pancreatic oxygenation, pancreatic pH, T.M.U. structure and function, local metabolic situation, pancreatic preconditioning and EBD investigation.

The pancreatic-gastric aspecific reflex

In order to apply the QBS method in bed-side diagnosis of diabetes mellitus, doctor has *at least* to know auscultatory percussion[22] of the stomach. Of course, for the accurate and exhaustive application of Quantum Biophysical Semeiotics, complete and safe knowledge of this method are required[23].

Auscultatory percussion of the stomach, essential in QBS, is performed as follows: in an individual in supine position and psycho-physically relaxed, placed correctly the bell-piece of the stethoscope upon skin projection area of the interested parenchyma, i.e. the stomach or the precordium – as indicated in Figure 1 – doctor applies *directly and gently* digital percussion with the pulp of middle finger, two times subsequently on the same point along radial, centripetal lines, starting a little far from the bell-piece of the stethoscope, moving thereafter towards it.

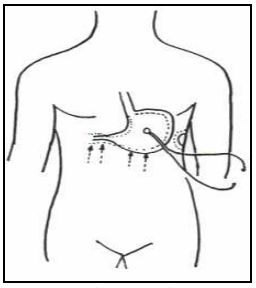


Figure 1

Interestingly, when digital percussion is applied directly on skin projection area of the great stomach curve, sound is perceived more intense, loud, hyperphonetic, and it seems "as originating near to doctor's ears". For our purpose, it is enough outlining only a short tract (2 cm) of the great curve of the stomach.

In healthy individuals, lasting pinching of the skin covering the costal margin – right or left – immediately beneath the sternum, i.e. 1-2 cm (VI thoracic dermathomere), brings about pancreatic gastric aspecific reflex (P.G.A.R.), namely dilation of both fundus and body of the stomach and contraction of antral-duodenal region, as indicated in Figure 1, exactly after 12 seconds of latency time (Lt): the degree of this *precious* parameter has to be evaluated carefully.

Other interesting parameters of the P.G.A.R., to be possibly (but not necessarily) considered are reflex-duration (physiologically, 4 seconds or less) and reflex-disappearing time or better *differential latency time* (physiologically, dlt: 3-4 seconds), identical to the so called *fractal dimension*, before the successive reflex. Interestingly, as regards the nature of

these gastric changes, biophysical-semeiotic signs are related to the structural and functional situation of microcirculatory bed of the investigated organ (Stagnaro 1997a, 1997b).

At this point, after a pause of 5 seconds, doctor evaluates for a second time the same parameters (*pancreas preconditioning*): in healthy individuals Lt appears to be 24 seconds or more, duration less than 4 seconds and dlt 3,5 - 4 seconds. In other words, degrees of parameters ameliorate clearly, in a statistically significant manner: *physiological preconditioning* of the pancreas.

As earlier described, in healthy individuals in post-absorptive state the Lt of P.G.A.R. is exactly 12 seconds, duration 4 seconds or less and, finally, disappearing time or dlt is 3 - 4 seconds (physiological fractal dimension - fD is 3,81), and in the preconditioning we observe better results, i.e., Lt appears ameliorated (Lt is 24 seconds or more).

In subjects, apparently in normal conditions, but really involved by hyperinsulinemia-insulinresistance - IIR and, therefore, with inherited real risk of diabetes mellitus and of all other pathologies, termed as *Metabolic Syndrome X* (Stagnaro 1986, 1993b), the degree of P.G.A.R. parameters are in relation to the severity of disorder. Therefore, these signs proved to be interesting from diagnostic point of view. At first, basal Lt is less than 12 seconds and duration 4 seconds or more.

Interestingly, dlt, i.e., *fractal dimension*, results less than 3 seconds. Of course, the intensity of changes are strictly correlated with the impairment of glucose metabolism and, consequently, with insulin-secretion and insulin-resistance.

In case of a hyperinsulinemia-insulin-resistance, evolving *slowly* towards diabetes mellitus, Lt gradually decreases, as well as dlt, whereas duration augments as far as diabetes mellitus, by degrees, appears after a lot of years.

Finally, diabetes mellitus can easily be diagnosed, even in clinically silent patients: basal Lt of P.G.A.R. is 9 seconds or less; duration is more than 5 seconds and dlt is 1-2 seconds (fD = 1 seconds is a topological and not *fractal* dimension), while pancreatic *preconditioning* results *pathological*, i.e., their parameters – particularly Lt – do not ameliorate or anyway they decrease in a statistically significant manner.

Pancreatic - Gastric Aspecific Reflex (P. G. A. R.) mean - intense digital pression on VI thoracic dermathomere (pancreas trigger points)

Latency time (Lt) in seconds	Latency time* after preconditioning (pause of 5 sec.)	MFR in seconds (reflex duration)	dlt- fD & equilibria	EBD	Preconditioning	Diagnosis
Lt = 12 (intensity < 2cm)	Lt = 24	3< MFR ≤4 (3.5<MFR≤4)* normal MFR, associated activation, outcome +; caecal and gastric reflex	4>fD ≥ 3 (ideal value fD=3.81) strange attractor	Normal EBD physiological function, increase of pancreas volume (Lt=2; duration=10) histangic acidosis	Type I Physiological tissue microvascular unit	Health
Lt < 12	Lt < 24	MFR ≥ 4 compromised MFR, dissociated activation, outcome ±	2<fD<3 limit cycle	Normal, slightly modified EBD function, small number of pathological EBD	Type II A Intermediate tissue microvascular unit; hyperinsulinemia-insulinresistance	Diabetes Mellitus Inherited Real Risk, Metabolic Syndrome X
9 <Lt <12	18 ≤ Lt < 24	4<MFR ≤ 5 growing compromised MFR, dissociated activation, outcome ±	1<fD≤2 limit cycle	Modified EBD function, increasing number of pathological EBD	Type II B Intermediate tissue microvascular unit	Diabetes Mellitus Inherited Real Risk in evolution
Lt≤9	Lt < 18	MFR>5 absent MFR, dissociated activation, outcome –	fD=1 fix point	Normal EBD function pathological, large number of pathological EBD	Type III Pathological tissue microvascular unit	Diabetes Mellitus

Table 1. Legend: MFR (Microcircular Functional Reserve); EBD (Endoarteriolal Blocking Device); fD (fractal Dimension); Lt (Latency time); dlt (differential latency time)

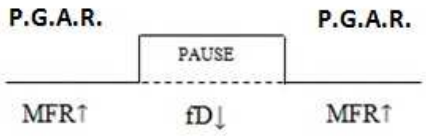
Pancreatic pH

According to clinical and experimental evidences (Stagnaro, 2004a), tissue pancreatic pH is related to the reduction of latency time (Lt) and to the extension of the duration of the P.G.A.R., which expresses the local MFR - microcirculatory functional reserve. MFR is inversely proportional to fractal dimension (fD), calculated as simply as the disappearing time of P.G.A.R. before the appearance of the next one (Scheme 8).

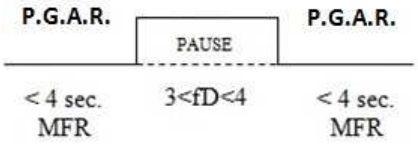
Summarizing, fD is directly (d) or inversely (INV) related to:

A) (d) the local MFR (vasomotility and vasomotion);

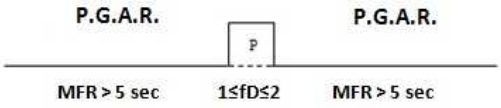
B) (d) the presence, or not, of type II DM or inherited Real Risk of diabetes (Scheme 10);
C) (d) the Lt of P.G.A.R. and then to tissue pancreatic pH (Table 1);
D) (INV) P.G.A.R. length (Scheme 9, Scheme 11).



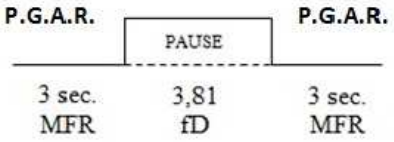
Scheme 8. MFR and fD are inversely correlated



Scheme 9. Physiological MFR – healthy state



Scheme 10. "T2DM" and related fD



Scheme 11. An optimal MFR and physiological fD

Tissue Microvascular Unit

According to Tischendorf's concept of Angiobiotopie (Curri, 1986), biological tissue-microvascular system can be described as formed by single units: the tissue-microvascular units.

In its turn, the tissue-microvascular unit (T.M.U.) is made up by three fundamental components:

1) *microvessels*, diameter < 100 μ,
2) *the blood*, flowing in them,
3) *perivascular connective*, periangium, interstitium or "environment" in which microvessels are placed, formed by water, free- and bound- water, cells and connective fibbers, and interstitial matrix, glucosamino-glycanes.

Microvessels can be subdivided as follows (Pratesi, 1990):

1) *Para-microcircle*: small arteries and arterioles, according to Hammersen, venules of I, II, III order, shunts or Arterio-Venous Anastomoses (AVA), functionally speaking (Bucciante, 1949);
2) *Microcircle*: nutritionnel capillaires, post-capillaires veinules, "meta"- artérioles.

With the aid of QBS, doctor is able to evaluate, in dynamic manner, T.M.U. of every biophysical system, from both structural and functional view-point, according to a synergistic[24] pattern, i.e. the clinical evaluation of microvascular dynamics.

Notoriously the microvessels carry on a motor activity, autochthonous and deterministic chaotic, which represents one of the most remarkable manifestations of microcirculatory hemodynamic, characterized by a *flow-motion* and hematocrit rhythmically fluctuating due to the particular behaviour of both *vasomotility* and *vasomotion*[25].

The oscillations of "upper" reflexes define the vasomotility – the general dynamics of microcirculatory vessels, while those of "lower" one express the vasomotion – capillary-veinules dynamics (Figure 2).

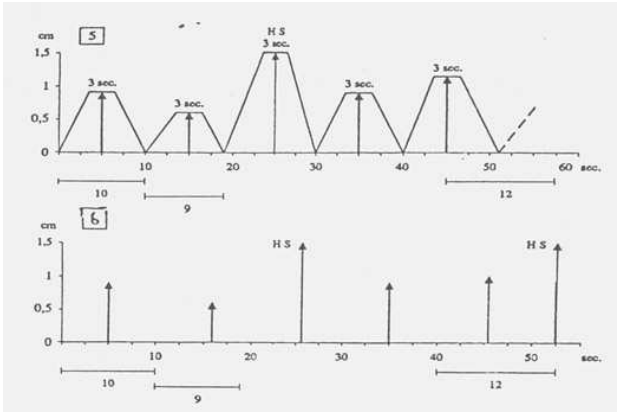


Figure 2: Physiology fluctuations of upper and lower urethral reflexes, at rest (vasomotility and vasomotion); HS stands for Highest Spike or highest oscillation

A biological system, as the tissue-microvessel system, so much highly evolved and well differentiated, as regards anatomy and physiology, can not react to attacks, different in origin, which involve it, by a lot of ways.

As far as tissue-microvessel unit is concerned, cells, transformed in *smooth muscle cells* and in *ramified smooth muscle cells*, when stimulated, either contract or dilate, although there is a residual possibility of further response.

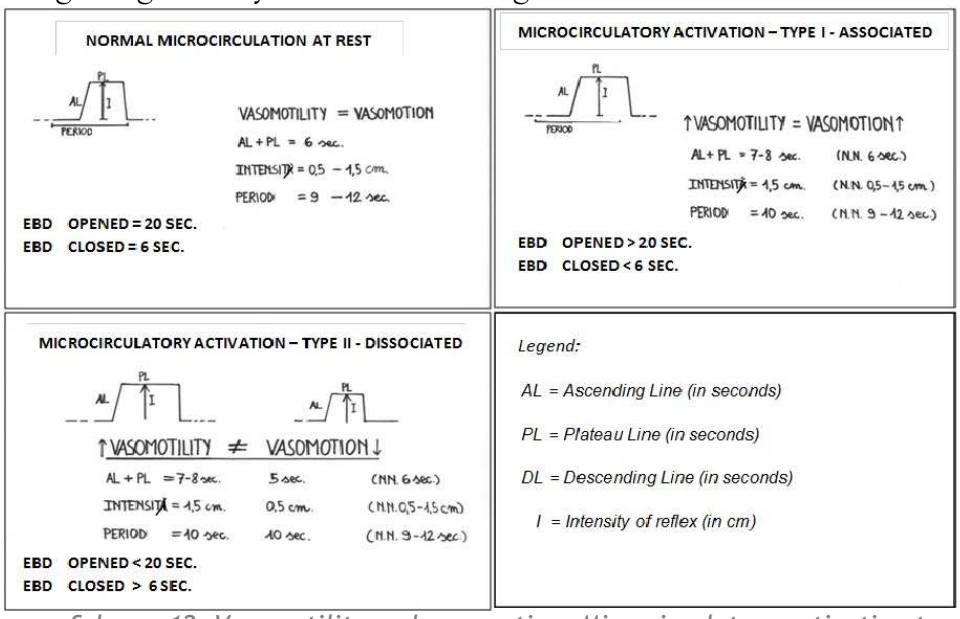
On the contrary, smooth muscle cells of the media of great arteries – elastic and muscular – which are less differentiated, react to various stimuli, even, de-differentiating and, then, evolving towards cells with secretors activity (Simonescu 1990, Gimbrone 1997).

These concepts account for the reason of the restricted number of tissue-microvascular unit reactions, doctor can observe at the bed-side by biophysical semeiotics and Clinical *Microangiology*[26].

The normal microcirculation at rest can become physiologically *active* when the parenchyma starts to work. The important set of micro vascular dynamic events, related to *microcirculatory activation - M.A.*, can be subdivided in three types (Scheme 12):

- type I or "associated", "physiological", in which both the *vasomotility* and *vasomotion* result increased and consequently blood-flow in nutritional capillaries and post-capillary-venules is augmented, due also to right AVA reaction; (e.g. during parenchyma work);
- type II or "dissociated", "pathological", in which the *vasomotility* shows increasing of both intensity and oscillation duration, while the *vasomotion* shows a highly differentiated behaviour, in relation to the presence of microcirculatory "compensation" or "decompensation" (failure), as we will say later on. (e.g. during pathological conditions);
- type III or "intermediate", when vasomotility is activated, while vasomotion shows basal activity, and hemoderivative structures are not activated. The transition from type I to type II goes through numerous intermediate stages, which from the

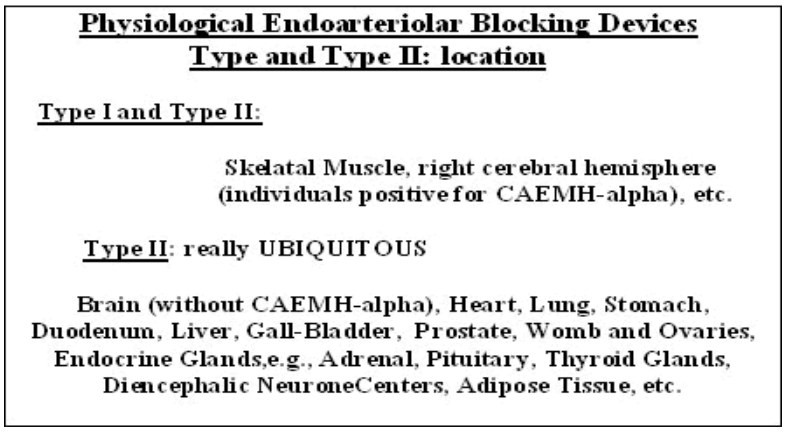
compensation reach the total irreversible decompensation of microcirculation, showing a large variety of different and significant forms.



Scheme 12. Vasomotility and vasomotion. Microcirculatory activation types

M.A. - type I shows the increasing of oscillation waves: the sum of AL[27] (ascending line) and PL[28] (plateau line) duration is equal to 7-8 seconds, maximal intensity (1.5 cm) as well as a period of 10 seconds. Arrows indicate the activation[29] of both vasomotility and vasomotion. Consequently, fractal dimension appears clearly reduced (Scheme 12). The under curve area "shows" microvessel sagittal surface during their highest and prolonged opening phase so that, under such condition, microcirculatory blood-flow is greatest.

Among microcirculatory structures, a primary role in the microvessel blood-flow is played by Endoarterial Blocking Devices (EBD), which are largely present in human body (Scheme 13).



Scheme 13: Doctor who knows the exact location of physiological type I EBD (skeletal muscle, right hemisphere of individuals CAEMH-positive, conjunctival mucosa) can recognize in easier way the type I pathological DEB, that play a pivotal role in diagnosing QBS real risk of most common and serious human disorders

Both physiology and anatomy of EBD, evaluated "clinically" for the first time, play a primary and pivotal role in diagnosis and prevention of the most common and serious

human diseases, including diabetes, hypertension, ATS, CVD, and cancer, permitting, for the first time "clinically", to define the link existing between *genetic* factor and *phenotype*, according to the theory of Angiobiopathy (Stagnaro, 2004).

EBD, derived from arteriolar medial layer, and located in a single point of vascular wall with two (arterioles) or more (small arteries, according to Hammersen) layers of smooth muscle cells, protruding to the lumen, show very different structure and form, under physiological and pathological conditions: small cushions with wide base, polyploidy formations, generally pedunculated, sphincteric formations, intimal contractile architectures (Figure 3).

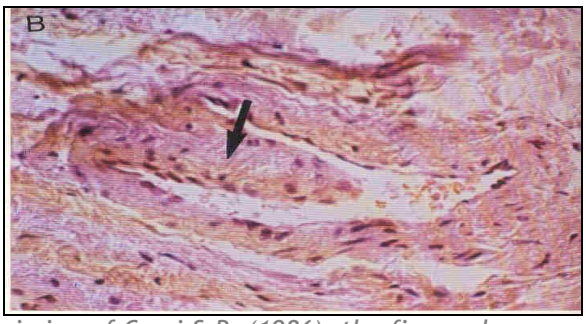


Figure 3. For kind permission of Curri S.B. (1986), the figure shows a refined imagine of EBD with a large base of the type "proboscide"

They are ubiquitous since they are located in all biological systems; more precisely speaking, only type II, normal, EBD, localized in arterioles, according to Hammersen, are ubiquitous. EBD are playing a primary role in the regulation of local microcirculatory *flow-motion*, as the following clinical evidence demonstrates: when abnormal, at least from functional biophysical-semeiotic viewpoint, EBD bring about impairment of MFR, which contribute to conditioning the "real risk" of disorders, like CAD, whose onset will possibly occur after years or decades.

EBD contraction, i.e. the contraction of its muscular cells, at the base of mean urethral reflex (arteriolar opening), brings about blood flow increase in the capillaries, microcirculatory stasis and, then, if lasting, possible hypertensive damage of related capillary net, and subsequently dilation at first, and, thereafter, basal membrane thickening. In case of microcirculatory activation type I, associated, EBD contribute significantly to increasing matter-energy-information supply to parenchyma, according to the physiological behaviour.

Diabetes Mellitus is somewhat very different from the "simple" pathological increasing of glycaemia and it is possible now to recognize since birth-day individuals at "real" risk of this metabolic disorder, *conditio sine qua non* for the "primary" prevention of type T2DM (NIDDM) and consequently of its dangerous complications.

We can so differentiate the *glycaemology*, in which we are not concerned, from the *clinical dialectology*.

The very initial stage of whatever "*degenerative*" disorders begins really as microcirculatory modifications, both functional and structural, particularly at the level of

EBD of related biological system, that in the course of years will be involved by the disease itself (Stagnaro, 2004a).

In addition, these microcirculatory alterations, well localized in a gland, apparatus, organ, only apparently "healthy", can be evaluated at the bed-side in a "quantitative" manner, permitting thus the therapeutic monitoring of interesting *pre-pathological* conditions, characterizing the "*grey zone*", the real site and moment of "primary" prevention, located between the "*white zone*" (physiology) and the "*black zone*" (pathology).

From QBS constitutions we can see that *genetic* factor reveals in both parechymal and related microangiological level, allowing doctor nowadays to assess this pathological symptomless condition, starting from the first decade of individual life.

The "mean" intensity stimulation of trigger-points of VI thoracic dermathomere – in practice, the skin of epigastrium immediately below costal arch at right and/or at left, about 5 cm away from sternal angle, where are localized *the pancreatic trigger-points* – brings about pancreatic-"middle" urethral reflex, which permits the assessment of both structure and function of EBD, located in pancreatic small arterioles and arterioles, according to Bucciante (1949): in individuals involved by diabetic constitution and in those with "real" diabetic risk, in IGT-subjects, and, of course, in "all" diabetic patients, such microcirculatory structures show abnormalities since birth-day, revealing alterations of different severity, varying from patient to patient.

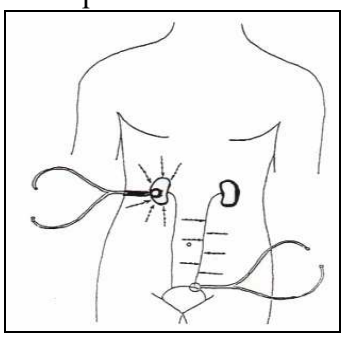


Figure 4

Figure 4 shows clearly the correct location of the bell-piece of stethoscope and lines upon which must be applied digital percussion, direct and light, in an individual in supine position, psycho-physically relaxed, in order to outline the limits of kidneys and urethras cutaneous projection area.

In case of diabetic constitution, in fact, pancreatic EBD show opening duration (duration of the "middle" urethral reflex) < 20 sec. (NN = 20 sec.) and/or closure duration (duration of the reflex disappearance) > 6 sec. (physiological value), which becomes particularly intense during stress tests, as the *test of two pressures*, which is easy to perform also by physicians with scarce experience in Biophysical Semeiotics: firstly, doctor has to evaluate the diverse reflex parameters during stimulation of pancreatic trigger-points, by a lasting pinch of "mean" intensity. Then, after an interval of at least 10 sec., he assesses for the second time the identical parameters during "intense" stimulation, that activates physiologically the pancreatic microvessels, bringing about, speaking technically, according to *Clinical Microangiology* terms, associated microcirculatory activation, type I[30].

In subjects at "real" risk of diabetes mellitus, the duration of EBD opening does not modify (NN > 20 sec.) or ameliorates in a not statistically significant manner, while the duration of closure does not become shorter (NN < 6 sec.).

These very interesting EBD modifications, caused by diverse stresses, aim to increase the blood supply to the histangium of pancreatic isles, thus providing pancreatic isles with matter-energy-information, and, obviously, they play a major role in the activation of the Microcirculatory Functional Reserve (MFR).

Interestingly, a further tool of assessing local MFR, always present in healthy tissue, is the *biophysical semeiotic preconditioning,* easy to perform, especially by doctor with poor experience in the new physical semeiotics.

During M.A, *type I, associated,* EBD are "open" mean urethral reflex, brought about by "intense" digital pressure on the pancreatic trigger-points, lasts for > 20 seconds (at rest, "mean" digital pressure, NN is 20 seconds), i.e., for a time longer than that observed at baseline, and, moreover, reflex disappearing (EBD de-contraction, expressed by reflex cessation from biophysical-point of view) is < 6 sec. (NN = 6 seconds). These physiological and functional "vasomotion" modifications aim to increase the blood-flow in nutritional capillaries of arterial wall external, outward third and, consequently, to remove efficaciously H^+ as well as various catabolites.

On the contrary, M.A., type II, dissociated, in which *vasomotion* is reduced, is always associated to EBD dysfunction, indicating pathological local microcirculation: *microcirculatory bad distribution of blood flow*[31], according to S.B. Curri (1986).

In M.A., type II, dissociated, pathological, "intense" digital pression, "middle" urethral reflex lasts for < 20 sec. (at rest, "mean" digital pression is < 20sec. too, while NN is 20 sec.) and then disappears for > 6 sec. (at rest > 6 sec., NN = 6 sec.), indicating a shorter "opening", i.e. contraction, and a prolonged "closure", i.e., relaxation, of EBD, and consequently reduced capillary-venular blood-flow in Langheran's islets (Figure 1): it occurs the microcirculatory phenomenon of the so-called "blood-flow centralization", due to the greater opening of AVA, and subsequent removal of capillary blood, we observe an insufficient blood-flow to parenchyma, that flows mostly in AVA, shunting therefore it away from parenchymal cells: this is a sign of diabetic constitution and inherited real risk of T2DM.

For instance, in case of chronic arteriopathy, arteriosclerotic as well as of other origin, it is present the *dissociated type of activation*, which brings about tissue acidosis, recognized at the bed-side by caecal, gastric aspecific and upper urethral reflexes.

M.A., type I, associated, physiological, event secondary to the increased demand of blood supply from the related tissue in a stage of activity greater than normal, indicates an emergency or stress situation, as regards the biological system in a precise moment (Caramel, 2010a).

Symptomless obstruction of a large arterial vessel (50%), for example, represents an *emergency* situation as far as biological system downstream is concerned, even at rest, which worsens obviously during physical activity, also slight.

In practice, such as condition influences favourably both the diagnosis and the prevention. For instance, in a patient "at rest", involved by "silent CAD", who does not

present any clinical phenomenology, the "light" digital pressure, applied on cutaneous projection area of right or left ventricle, allows doctor to recognize the *microcirculatory activation, type I, associated,* by urethral reflexes evaluation, indicating the symptomless coronary pathological condition.

Among numerous and different clinical-microangiological tools, a primary role is played by QBS diagrams, "microvascular" as well as "macrovascular", which can be subdivided in five groups:

1) tissue-microvascular unit - T.M.U. – diagram (Figure 5);

2) lymphatic diagram (Figure 9);

3) venous diagram;

4) arterial diagram;

5) various biological systems diagram: cardiogram, renogram, pancreogram, hepatogram, surrenogram, a.s.o.

Interpreting correctly and utilizing properly *the urethral reflexes*, it is possible to transform in a "geometrical" way the deterministic-chaotic activity of microcircle of all biological systems, under both physiological and pathological situations, giving, thus, an innovative way to "clinical" investigation of T.M.U. structure and function, and consequently of related parenchyma. Beside this biophysical-semeiotic method, there are a large variety of bed-side assessments of blood circulation in peripheral arterial vessels, more difficult to perform, but really refined.

For instance, the evaluation of the microcirculation in the pulps of toes is done as follows: in healthy, in supine position and psycho-physically relaxed (with open eyes), digital pressure of "light-moderate" intensity, applied upon the pulp of a toe, brings about gastric aspecific reflex lasting for 6 seconds, after a Lt of 6 seconds, intensity about 1 cm, and three subsequent re-enhancements, followed by *tonic Gastric Contraction* (*CGt*). Soon after the rapid interruption of the stimulation, after only 2 seconds the stomach reaches the basal volume and subsequently appears a small gastric aspecific reflex – G.A.R., *Z wave*, indicating elasticity of microvessels wall, as shown in *T.M.U. diagram* (Figure 5).

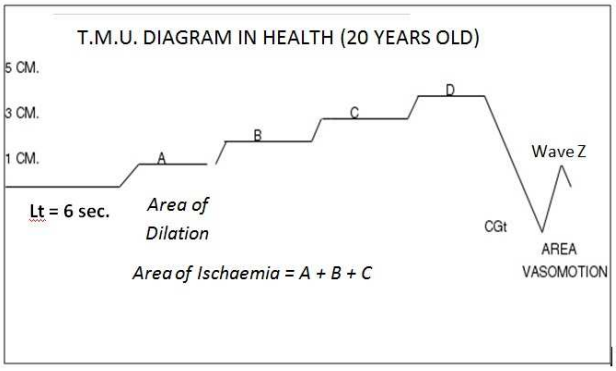


Figure 5

Interesting to observe are the Lt of 6 sec., the horizontal line at the top of *Dilation Area* (*AD*), the absence of Acidosis *Critical Point* (*CP*) of 5 cm, and the definite *Z wave*.

Beyond glycaemia: QBS evaluation of glycaemic metabolism

Half of patients with type 2 diabetes mellitus (95% of all diabetes cases) are nowadays undiagnosed, although the assessment of glycaemia in unfasted individuals is to-day routine investigation. Therefore, in the war against diabetes we must go "beyond glycaemia".

The QBS methods, described in this paper, are based on capillary altered permeability, present at base-line, or in initial phases during dynamic tests, detectable in DM starting from "diabetic constitution".

Beside the well-known *diabetic microangiopathy* of overt cases, characterized by structural alterations involving type II AVA, B group, according to Buccciante (1949), and, as we demonstrated, by EBD genetically dependent modifications, it does really exists capillary altered permeability, secondary to endothelial as well as perivascular matrix disorders, caused by CAEMH-α (Stagnaro, 1986). These clinical data are in perfect agreement with those of other authors, who demonstrated endo-capillary increasing even in the first stages of DM, before microangiological structural alteration, notoriously and obviously worsened by successive metabolic alterations (Sandeman, 1992).

In reality, the increasing of blood insulin level, present in those stages preceding for years and decades diabetic manifestations onset, brings about venular-capillary pathological permeability (Zenda, 2003). Both diabetes and IIR cause endothelial dysfunctions, including the augmentation of permeability (Feener, 2001), which plays a pivotal role in patho-physiology of cardiovascular diseases.

Formerly, it has been demonstrated that tissue acidosis plays a primary role in provoking microvascular damage; such as negative action is already present at birth, i.e., years or decades before the occurrence of whatever sign of retinopathy and nephropathy, in agreement with other authors (Ditzel 1968, 1975). Caused by CAEMH-α, histangic acidosis, through capillary pathological dilation (high *A Phase* in T.M.U. diagram) provokes increasing of capillary permeability that in diabetic patient is correlated with the severity of glycaemic values.

As a matter of fact, in overt disease, we observe reduction of blood supply and increasing of oxygen consumption. Consequently, under these metabolic conditions, the genetically-dependent histangic acidosis, which acts in negative manner on vascular permeability, is further augmented and thus capillary permeability appears worsened (Ditzel, 1975).

At this point, we must remember that obesity, associated very often with IIR, is correlated with low-grade inflammation, nowadays regarded as a progression factor of arteriosclerotic process (Mohamed-Ali, 1997); partly, such as association may be explained by the increasing of adipose tissue in subjects with metabolic syndrome. Adipose tissue, an intern secretion organ, produces cytokines, like IL-6, among other substances, which increase by itself capillary permeability.

QBS allows doctor to evaluate, not only the present "glycaemia", correlated with capillary altered permeability, but also efficaciously insulin secretion (stress tests and

pancreatic preconditioning), insulin receptor sensitivity in various peripheral organs, lipid dysmetabolism in individuals involved by "diabetic" and "dyslipidemic" constitutions, *conditio sine qua non* of T2DM occurrence.

Quantum Biophysical Semeiotics allows doctor to study all aspects of glucose metabolism: insulin secretion, tissue hormone function (insulin receptor sensitivity), glucose up-take and, respectively, glucose hepatic disposal in *absorptive* and *post-absorptive state*, lipid metabolism, and present glycemia.

In fact, glycaemic values (i.e., blood glucose levels) affect capillary permeability, modifying it even in initial *diabetic* stages, e.g., hyper-insulinemia – insulin-resistance, and notoriously in overt diabetes, whose pathogenetic mechanisms are explained by the authors in really different ways (Stagnaro 1993a, TRG 1993, Ditzel 1968, Curri 1968, Pratesi 1990, Stagnaro 2002, Ditzel 1975, Feener 2001, Zenda 2003).

According to Stagnaro works, in the venular-capillary permeability – an especially complex event (Pratesi, 1990) - a pivotal role is played by CAEMH-α-dependent histangic hypoxia (Stagnaro, 1986), as the following clinical and experimental evidence suggests: in healthy, but CAEMH-α-positive, latency time (Lt) of G.A.R. (Figure 6), caused by "light" digital pressure, applied on inner brachial surface (selective compression of superficial lymphatic vessels: Lymphatic Gastric Aspecific Reflex – L.G.A.R.) is 10 seconds (NN = 10 sec.); subsequent reflex reinforcement, or increasing, appears clearly after further 10 seconds as shown in Figure 6 (Stagnaro, 1998).

Really, as it has been demonstrated "clinically" in earlier article (Stagnaro, 1986), capillary permeability is altered a long time before hyperglycaemia occurs, according to other authors, who showed it with the aid of different methods (Ditzel 1975, Feener 2001), due to always present CAEMH-α, that affects both endothelial cells and the cells of peri-vascular matrix, taking part in glucosaminoglycanes synthesis (Curri 1968, Pratesi 1990). CAEMH-α represents the *conditio sine qua non* of T1DM and T2DM (Stagnaro, 1986).

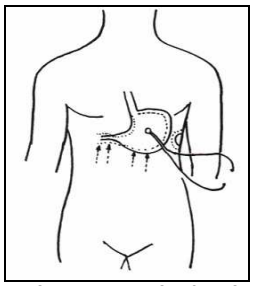


Figure 6: Gastric aspecific reflex: in the stomach, both body and fundus are dilated, while the antral pyloric region contracts.

By contrast, reflex Lt (Figure 9) lowers to 5 seconds (NN = 10 sec.) in both decompensated diabetes, Bilancini-Lucchi's Sign (Stagnaro, 1993a), and, in case of healthy, CAEMH-α-positive, but after more than 10 seconds of insulin secretion interruption, for instance, by "intense" stimulation of pancreas trigger-points (lasting and intense cutaneous pinching of VI thoracic dermathomere), or during stimulating melatonin secretion and/or SST-RH (Stagnaro, 1997b) as shown in Table 2.

QBS METHODS OF GLYCEMIA EVALUATION
LYMPHATIC DIAGRAM (BILANCINI-LUCCHI'S SIGN) *basal and after-stress-tests*
TISSUE-MICROVASCULAR UNIT DIAGRAM OF DIGITAL PULP *basal and after-stress-tests*
INSULIN SECRETION AND PANCREATIC AND PERIPHERAL MICROCIRCULATION ASSESSMENT

Table 2

Stagnaro is carrying on studies, whose present data are really promising, which aim to "quantify" the reduction of the Lt of aforementioned reflex after "standard" (10 seconds) inhibition (impairment) of insulin secretion, a) in healthy, without CAEMH-α and with CAEMH-α, b) in subjects involved by "diabetic constitution", c) in case of Grew Zone or pre-morbid Zone, d) in Metabolic Syndrome, with and without the presence of slow diabetic evolution. Obviously, such as evaluation must be applied after exclusion of whatever oedematous disorders of the arm.

In assessing the present glycaemia with the aid of the original semeiotics, the "Tissue-Microvascular Unit - T.M.U. - Diagram" of digital pulp plays a pivotal role, as it is described as follows[32]. As regards the evaluation of glucose blood level (glycaemia) by means of QBS, all tests causing transitory lowering of insulin secretion modify pathologically the "physiological" diagram, which becomes that typical of diabetic various phases, corroborating the reliability of employed method: Lt lowers to 5 seconds (NN = 6 seconds), *A Phase* becomes large and closed at the top characteristically by "ascending" line, acidosis Critical Point (CP) of 5 cm appears in *D Phase*, *CGt* occurs rapidly, and *Z wave* disappears.

In the patient with "initial" Impaired Glucose Tolerance - IGT, "basal" diagram of T.M.U., but not that observed during stress tests, shows a normal latency time yet (NN = 6 sec.), while during both stress tests and various IGT phases in slow diabetic evolution, when insulin secretion is impaired (Figure 7), Lt lowers to 5 seconds (short-time, isolated episodes of hyperglycaemia, particularly post-prandial). *A Phase* is characterized by large *Dilation Area* (*DA*) ≥ 1 cm. (i.e., capillaries dilated NN ≤1 cm., in an age-dependent way): gastric aspecific reflex shows intensity ≥ 2,5 cm., realized in 1 seconds, as α angle > 45° demonstrates.

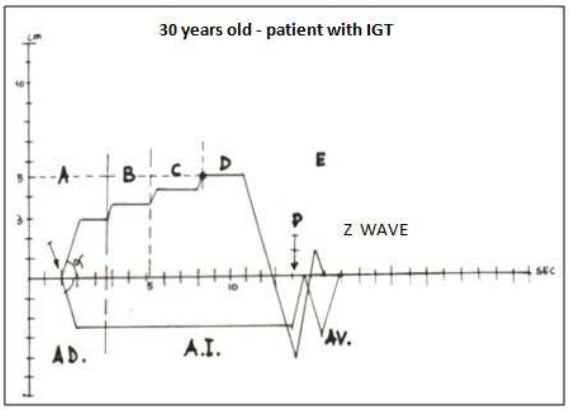


Figure 7

Interestingly, α angle is > 45°, indicating *A Phase* rapid occurrence, showing upper line physiologically "horizontal". Microvessel dilation, as consequence of hypoglycaemic episodes, caused by hyperinsulinemia (values observed 3 hours after meal, i.e., in the *post absorptive stage*) disappears, in fact, after *apnea test* of 5 seconds duration (sympathetic hypertonus reduces insulin secretion). Such as microvessel modification aimed to the tissue normal supply of O_2 and substrates.

In fact, the subsequent three phases show a completely physiological behaviour: in fact *A Phase* closed at the top by an horizontal line and critical point *CP* (*CP* = 5 cm) is in *D Phase*; duration of single *Phases B*, *C*, and *D* equal to 6 seconds; *CGt* appearing latency time is slow (2-3 sec.) and *CGt* disappearing Lt is quick (2 sec.) as well as the presence of *Z wave* indicate that tissue-microvascular unit is slight suffering from the morphological view-point - Ditzel's (1968) *functional diabetic microangiopathy*.

At this point, doctor must obviously examine carefully all QBS signs reliable in rapid recognizing IGT: Lt duration of gastric aspecific reflex - G.A.R. >12-13 seconds under hyperinsulinemic condition, pancreatic preconditioning, assessment of vasomotion – both pancreatic and peripheral – in *post-absorptive state* and *absorptive state*.

In this stage of glucose metabolism – in the diagram, *CP* of 5 cm is located in *D Phase* and *Z wave* is present (physiological capillary elasticity) – a correct, proper diet, etymologically speaking, discontinue, let come back, the alterations of T.M.U. diagram, particularly in most favourable cases.

Contemporaneously, we observe the regression, until the disappearing, of QBS numerous signs of initial phases of diabetes mellitus.

In fact, *insulin receptor sensitivity* return to normal value (pancreatic and peripheral vasomotion are the same), when real body weight parallels "ideal" body weight, and *histangic acidosis* and/or the *alterations of lipid metabolism*, independent of actual lipidemic values, assessed with the aid of QBS (preconditioning of abdominal adipose tissue), always present, even of small intensity, due to negative lipid action (particularly triglycerides) on insulin receptor sensitivity.

T.M.U. Diabetic Diagram (IDDM and NIDDM)

Diabetic diagram, which allows by itself to diagnose diabetes at the bed-side, is characterized by Lt of 5 seconds (NN = 6 sec.), slow carrying out of G.A.R., which persists for *A Phase* duration if diabetes is *decompensated*, i.e., 6 seconds (stiffness of microvessel wall due to PAS-positive substance storage and local connectivization events) associated with pathological modifications of interstitial amorphous matrix (Figure 8).

In addition, diabetic diagram shows an *intense* A Phase, indicating capillary dilation. Typically and, therefore, interestingly, "ascending" line (AL) at the top of *A Phase* persists in relation to glycaemic levels: in case of *metabolic decompensation* when glycaemia is higher than normal; the highest duration is 6 seconds (Figure 8).

Consequently, diagnostic value of diabetic diagram is really noteworthy: typical is the slow, "ascending" line, at the top of *A Phase*, which continues in *B Phase* by degree, in a

smooth manner, in absence of "horizontal" A line. This behaviour is characteristic of both T1DM and T2DM, if glucose blood levels are pathological.

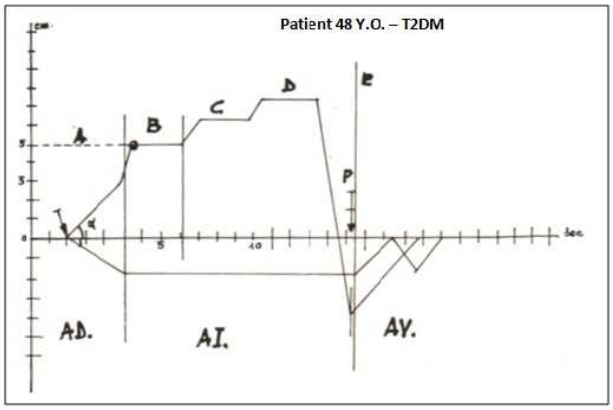


Figure 8

In a patient, 48 years old, with T2DM, Figure 8 shows a G.A.R. with Lt less than 6 seconds, *A Phase* with the typical ascending line at the top related to raised glucose blood levels, CP (°) location in the *B Phase*, whose duration is less than 6 seconds (important parameter value at bed-side, assessing glycated proteins), intense Dilation Area (AD) as well as Ischemia Area (AI), severe impairment of Vasomotion Area (AV). Noteworthy, are in particular the typical behaviour of slow carrying out of G.A.R., showing a Lt of only 5 seconds, and the "ascending" line at the top of *A Phase*, characteristic sign of overt diabetes mellitus: its duration is related to the arising of glycaemia. Under abscissa is referred the behaviour of cholecystic-choledocic reflex.

In case of T1DM and T2DM, DA intensity is ≥ 2 cm (NN = 1,5 cm), due also to the store of interstitial amyloid, and it is closed at the top by "ascending" line, becoming more steep in the terminal tract, since physiologically horizontal line of *A Phase* is absent, in relation to the severity of diabetic syndrome.

Consequently, α angle appears to be $< 45°$. The Critical Point is located towards diagram left side, in initial part of B, and it is always exceeded by subsequent reinforcing of G.A.R.: diagram "verticalization with shifting to the left", "aspecific" pathological sign. Obviously, associated ATS increases the pathological "verticalization with shifting to the left of diabetic diagram of tissue-microvascular unit.

Easy to understand, remarkable appears the impairment of Vasomotion Area (AV), even in case of a patient involved by NIDDM with glycaemia properly controlled only by diet (Figure 8): CGt does "rapidly" occur and "slowly" disappears (O_2RT or O_2 Recovery Time) for more than 2 seconds, after quick interruption of digital pressure; *Z wave* is absent.

Analogous is the behaviour of first phase of lymphatic diagram, Bilancini-Lucchi's sign, mentioned above, demonstrating internal and external coherence of biophysical-semeiotic theory: after a Lt < 10 seconds (NN = 10 seconds), in relation to DM severity, starting from the applying of "light" digital pressure on internal surface of arm middle third, G.A.R. appears, that forms lymphatic diagram, showing a slow, and prolonged realization, present since the initial phases of DM as shown in Figure 9 (Ditzel, 1968).

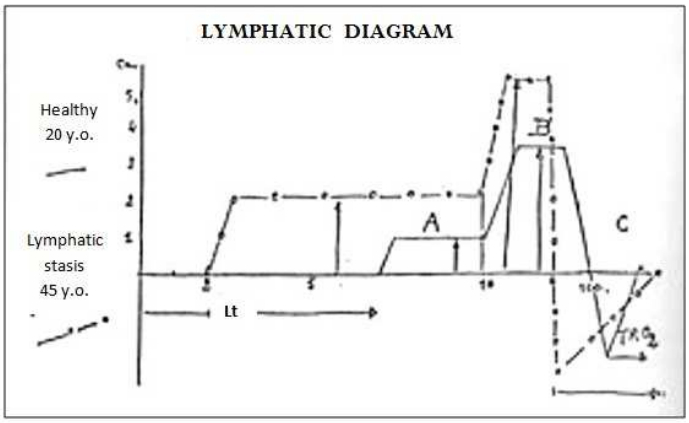


Figure 9

From "clinical" diagnostic view-point, T.M.U. diagram plays a pivotal role in T1DM (NIDDM) (Figure 10).

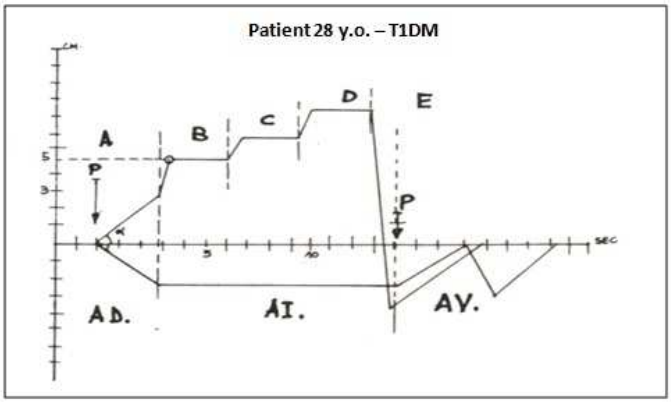


Figure 10

Figure 10 shows the T.M.U. diagram in case of T1DM. The behaviour of *A Phase* is typical with "ascending line" at the top, which becomes steef in the final tract. Interestingly, *B Phase* duration (NN = 6 sec.) appears reduced with indirect relation to the increase of glycated haemoglobin.

Once again, Lt is smaller than normal (< 6 seconds) and ascending phase of G.A.R. closes *A Area* at the top: it initially realizes slowly and, than, rapidly; quick final increasing is typical of diabetes mellitus as well as "severe" IGT, while α-Angle is < 45°. Dilation A is large, so that CP of 5 cm. is located in the first part of *B Phase* and later is abundantly exceeded: "verticalization with shifting to the left".

Duration of *B Phase* (NN = 6 sec.) is really interesting and gives a lot of information: it is shorter than normal value in inverse relation to diabetic metabolism impairment, i.e., as higher results glycated haemoglobin, in direct relation.

As a consequence of remarkable alteration of post-ischemic reactive hyperaemia, CGt realizes in less than 2 seconds (NN 2-3 sec.), and disappears "slowly" (TRO_2 > 2 sec.); finally, *Z wave* is absent (the patient, whose diagram is referred in Figure 10, was 28 year old!).

In other words, the illustrated diagram allows by it-self to diagnose diabetes mellitus, underlining a severe disorder of T.M.U., e.g., of digital pulp or ungueal nail-fold, caused by stiff and dilated microvessels (large DA), where, therefore, both microcirculation and gaseous exchange are greatly compromised: diagram "verticalization with shifting to the left".

At this point, it is useful to report an interesting datum regarding IDDM bed-side diagnosis, i.e., the absence of amyloid storage in the interstitium of Langheran's isles. As consequence of this fact, pancreatic-"in toto" urethral reflex show a normal intensity (< 1 cm.), in contrast to the above-mentioned observation in case of NIDDM (≥ 1 cm.).

In addition, the accurate evaluation of vasomotion, both in the pancreas and in peripheral organs (lever, skeletal muscle, central and peripheral adipose tissue, useful in clinical assessing insulin receptor sensitivity), allows doctor to recognize DM by means of clear-cut "discordance" of relative values of AL + PL duration in the *absorptive-state* as well as in the *post-absorptive state*.

Before concluding the illustration of T.M.U. "diabetic" diagram, it is necessary to underscore the correlation between Lt (NN = 6 sec.) and the duration of *A Phase* "ascending" line with present glucose blood level – with some extent – while *B Phase* duration (in seconds) (NN = 6 sec.) reveals an inverse correlation with glycated haemoglobin values, for the first time clinically assessed in a really reliable manner.

We avoid now and here to discuss the patho-physiological mechanisms, surely interesting, afore-mentioned relations are based on, useful from "clinical" view-point, preferring a "pragmatic" illustration. We must, however, state that Lt shortness and *A Phase* behaviour are correlated with capillary dilation and stiffness, as well as early store of interstitial amyloyd, secondary to the histangic disorder, caused by hyperglycaemia. Moreover, *B Phase* shortness (NN = 6 sec) is related to capillary basal membrane thickness, related in turn to glycation phenomena.

Behavior of vascular smooth muscle cells in healthy and IIR

In order to understand the relation between hyper Insulinemia-Insulin Resistance - IIR and cardiovascular disease, we must remember that IIR appears *exclusively* on the basis of CAEMH.

In healthy, *insulin secretion acute pick test* (Stagnaro, 1997a), i.e., the stimulation of pancreatic trigger-points (epigastrium skin below costal arch, at left and right, inside emiclavear line) by cutaneous pinch lasting for 12-14 seconds, brings about acute pick of insulin secretion as well as arterial "vasodilatation", e.g., of brachial artery: intense digital pressure, applied upon this artery, provokes "in toto" urethral reflex of 0,5-1 cm intensity; evaluated successively, a second time, soon thereafter *insulin secretion acute pick test* its intensity appears significantly increased: 1,5-2 cm. (Stagnaro, 1990).

Really, from clinical microangiological view-point, these events are more complex, articulated, fascinating than generally admitted, as the term "vasodilatation" permits to

understand: under physiological condition, in fact, insulinemic acute pick, beside arterial dilation, activates microcirculation, including that of *vasa vasorum* – type I, associated – and, therefore, Microcirculatory Functional Reserve (MFR), following, e.g., in myocardium, a clear-cut increased tissue O_2 level (Stagnaro, 1998).
In practice, by performing **QBS**, as far as coronary assessment is concerned, doctor can get information on myocardial oxygenation (Caramel, 2010a) as shown in Figure 11[33].

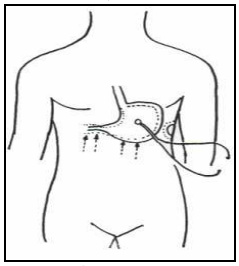


Figure 11

Successively, after precisely 3 seconds from the end of *insulin secretion acute pick test*, doctor evaluate a second time above-referred parameters (in practice, it is enough to assess only Lt), comparing new results with the former ones: in healthy, latency time arises to 10-12 seconds, showing increased myocardial O_2, due to the activation of coronary Microcirculatory Functional Reserve (MFR), caused by insulinemia (Stagnaro, 1997c).
As a matter of fact, the results are the same as those observed by coronary MFR stimulation by the aid of *two pressure test* (during the second stimulation, an "intense" digital pressure is applied on ventricular cutaneous projection area) or by Valsalva's manoeuvre.
On the contrary, in case of IIR, when basal parameters values of aspecific gastric reflex (in practice, Lt) are yet normal, at least in initial phase, during the second evaluation parameter values either appear unchanged or the result is altered (i.e., Lt is normal or reduced), in relation to the stage and seriousness of IIR, but, especially, to the abnormality of macro- and micro-vascular reaction, *genetically* induced, to "vasodilator" stimulation, followed by decreased tissue blood-flow and pH lowering (Stagnaro, 2004c).

In fact, in individuals *not yet* involved by IIR, but by pre-metabolic syndrome[34], and by "arteriosclerotic constitution", in whom is present inherited dysfunction of Endoarterial Blocking Devices (EBD) in *vasa vasorum* as well as in parenchymal tissue-microvascular system, where arterial and microvascular reactivity is abnormal, we observe the same results as those assessed under above-described experimental conditions.
From the above remarks, reader understands that IIR, which follows the former phase or Zero Stage or *pre-morbid, pre-metabolic Stage*, Grew Zone, enhances an abnormal, pathological macro- and micro- reactivity, genetically mediated.
At this point, we must remember that the increased blood supply to tissues, e.g., to skeletal muscle, augments parenchymal insulin and glucose uptake, explaining 40% glucose uptake hormone-mediated (Baron, 1990).
In healthy, insulin brings about "vasodilation" stimulating endothelial radical NO production; this hormone action is reduced or suppressed in "arteriosclerotic constitution", starting from the two first life decades, in obesity and/or NIDDM (Olefsky,1982).

To summarize, in patients with IIR, abnormalities of coronary and some other arterial vessels are possibly present, obviously, in relation to selective location of inherited functional-structural EBD alteration, to substances, which physiologically induce "vasodilation", as insulin.
On the base of such abnormal vascular reaction, which play a primary role in cardiovascolopathy onset, present from the two first life-decades of individual "at real risk" for CAD, there is EBD bad functioning of coronary *vasa vasorum*, as well as myocardial microvessels.
In fact, it is easy to recognize and evaluate this interesting, unknown situation of modified, e.g., coronary reactivity, both macro- and micro-vascular, present in the first two life-decades, by means of *heart preconditioning* (Stagnaro, 1997c) or in a more refined manner, i.e., by assessing directly coronary EBD function(Caramel, 2010a).

Pancreatic preconditioning and EBD

In healthy individuals – in supine position – digital pressure of mean intensity on the VI thoracic dermathomere brings about pancreatic gastric aspecific reflex[35] (P.G.A.R.) after a latency time (Lt) of 12 seconds. P.G.A.R. lasts less than 4 sec., soon thereafter disappears for 3-4 seconds. Disappearing time corresponds to *fractal dimension – fD* (Scheme 8). Afterwards, a second reflex occurs. The duration of P.G.A.R. unfolds the microcirculatory functional reserve (MFR) activity of related pancreatic microvessel, thus correlated with the function and anatomy of the microcirculatory bed, or Tissue Microvascular Unit - T.M.U.

At this point of investigation, the physician quickly interrupts the digital pressure for a length of exactly 5 seconds. Then, Lt and P.G.A.R. are evaluated again: Lt raises to 24 seconds or more, P.G.A.R. lasts less than 4 seconds, disappearing after roughly 4 seconds: these values evidence a *physiological preconditioning*.

In summary, physiological Lt of P.G.A.R. is 12 seconds at the first evaluation (*basal-line value*), but increases clearly in the second (is double) as well as in the third one, due to the physiological activation of MFR.

In individuals at risk of diabetes, Lt at *base-line* is less than 12 seconds during the first evaluation. P.G.A.R. lasts 4 sec. or more and disappears for less than 3 seconds: lowering of fractal dimension[36]. Moreover, preconditioning results "pathological", as Lt is less than 24 seconds: these values evidence a *pathological preconditioning.*

The above-described bio-physiological semeiotic method is proper for clinical preconditioning of almost every organs, it is proved to be useful and suitable for mass preventing or detecting ischemic heart disease, kidney disorders (including future stones), arteriosclerosis, even clinically silent, arterial hypertension, diabetes, cancer, and so on.

In healthy the *preconditioning* brings about, as natural consequence, an optimal tissue supply of material-information-energy, by increasing local *flow-motion as well as flux-motion* - preconditioning, type I. On the contrary, if real risk is present, *preconditioning* data are almost the same as the basal ones, but Lt is a little shorter than physiological one -

preconditioning, type II. Finally, in overt disease, *preconditioning* shows an altered and shorter Lt of reflex in relation to seriousness of underlying disorders - preconditioning, type III (Table 1).

At this point, we come back to the former example: in the initial phase of diabetes mellitus, which evolves very slowly toward successive phases, "basal" QBS data can "apparently" result normal. However, under careful observation, the duration of P.G.A.R. is equal or more than 4 seconds (NN < 4 seconds), indicating a local microcirculatory disorder.

Really, in these conditions, EBD function is clearly compromised, but for some time the increased *vasomotility* counterbalances efficaciously the impaired supply of normal blood amount to parenchyma: also the *vasomotion*, at rest, shows parameter values oscillating in physiological ranges, due to the augmented arteriolar sphygmicity. Noteworthy, from the diagnostic point of view, are also the pancreatic-caecal and -gastric aspecific reflexes, when accurately assessed: after a Lt less than 12 seconds, doctor observes a reflexes duration, before the successive one initiates, of 4 seconds (NN < 4 seconds), and a differential Lt (fD or duration of reflex disappearing before the beginning of the following) of just 3 seconds (3 < NN < 4).

Clinical recognizing of these "slight" abnormalities, really useful in diagnosing initial and/or symptomless disorders, although not difficult to perform, requests a good knowledge, a steady experience and a precise performance of the new semeiotics.

In these cases, *preconditioning* allows in simple and reliable manner to recognize the pathological modifications, mentioned above, which indicate the altered physiological adaptability, even initial or slight, of the biological system to changed conditions as well as to increased tissue demands. The various parameters of caecal, gastric aspecific and choledocic reflex, type of activation and, then, EBD function, related to a defined biological system, parallel and are consistent with the data of *preconditioning*.

Type 2 Diabetes Mellitus: prevention and therapy

Given the accumulating evidence that diabetes mellitus, whether silent or not, carries a poor prognosis in patients with known diabetes, it is justified to follow an active policy even in patients who are totally free of symptoms. Essentially, the rationale for the use of histangioprotective drugs (like L-Carnitine, Co Q10, Conjugated-Melatonin, a.s.o.) in patients with T2DM clinically silent, relates three premises: the favorable effects of these products on lipid and glucose metabolism, the positive influence of these drugs on pancreatic preconditioning, because they improve blood flow in pancreatic tissue microcirculatory units, and the improvement of pancreatic microcirculatory remodeling, e.g., lowering the number of newborn-pathological type I, subtype b) EBD, when histangioprotective drugs are utilized in early stage, in fact the intensity of specific middle urethral reflex significantly decreases under such treatment.

Practically, in order to ascertain clinically silent T2DM it is advisable to assess shape and intensity of low urethral reflex oscillations, i.e., vasomotion, as illustrated above

(Figure 2), which permits doctor to calculate the fractal dimension of pancreatic microvessels, i.e., deterministic chaos (3< NN < 4; ratio HS/Minimal oscillation, fD = 3), corresponding perfectly to the differential Lt of P.A.G.R., as well as the duration of this reflex (NN < 4 seconds) easily assessable (Table 1).

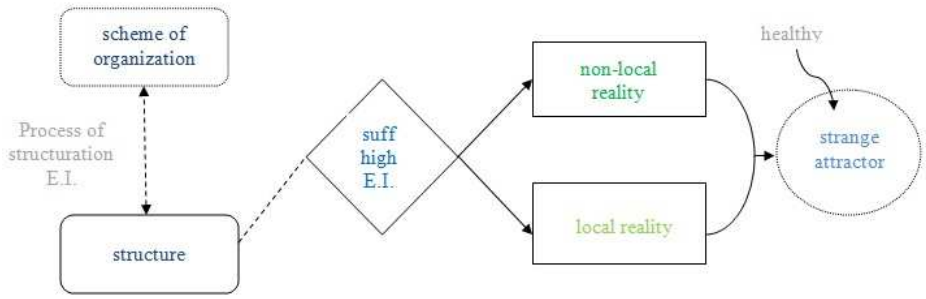
As far as pancreatic preconditioning is concerned, it is sufficient and hence advisable in day-to-day practice to assess the Lt of the second P.A.G.R., i.e., in the second evaluation, performed exactly after a pause of 5 seconds from the end of the basal evaluation: in health, latency time raises in a significant manner from 12 seconds (basal value) to 24 seconds, i.e., to doubly value.

From the practical viewpoint, both duration (NN < 4 seconds) and differential Lt, i.e., disappearing time (3< NN < 4), of pancreatic-caecum and/or -aspecific gastric reflex, i.e. fD, gives exhaustive information about pancreatic vessels morphological and structural situation, according to Angiobiopathy theory (Stagnaro, 2004).

Actually, important data are easily obtained also by means of the Lt of pancreatic-caecum and/or -aspecific gastric reflex, which informs about pancreatic oxygen supply: in health, during digital "mean" pressure upon cutaneous projection area of the pancreas, basal Lt value is 12 seconds. However, doctor must remember that in case of T2DM "real risk" and T2DM initial stage, such as parameter value is almost normal (less than 12 seconds), but reflex lasts 4 seconds or more (NN < 4 sec.), indicating diabetics pathological condition.

In conclusion, in a long, well-established, clinical experience, the above-described biophysical-semeiotic methods proved to be reliable, easy to perform on very large scale, useful, and suitable for detecting T2DM, even clinically silent or really initial, i.e. since inherited real risk of diabetes.

In absence of inherited real risk of diabetes (Scheme 14), all diabetes risks factors will be mere spectators, because that person will never be affected by type T2DM: pathologies and chronicity of this kind will never happen.



Scheme 14. Autopoiesis and Energy Information in absence of Inherited Real Risk of CAD

Scheme 14 shows that in human bodies there is physiologically the healthy co-existence of two different realities: local reality and non-local reality. The nonlocality disappears if the mitochondrial respiratory activity - and consequently EI – sensitivity decreases. For example Lory's experiment (Stagnaro 2008) fails, if is applied a stimulation in a subject following the apnea test, with the result of an impaired mitochondrial activity.

The compensation takes place because of nuisances involving dissipative structural changes, but always subject to the power system's inherent conservative autopoietic organization.

The congenital QBS Real Risk (RR) arises at an intermediate stage between the scheme of organization and the structure, a first structuration from the scheme (not observable) on which we can identify it (in case there was) using simple clinical tests at bed-side, in a vision in which if there were RR, it would be able to tend to a pathology (potential disease), a pathology which, if occurred, would amount to a fully structuration of the scheme of organization (e.g., genetic alteration of mit-DNA) to disease. RR, if pathologically evolving, is the slow eventing of disease events. Also considered in itself, whether static, is a manifestation of the structuring process of the organization. The process is reversible in the sense that through histangioprotective drugs like L-Carnitine, Co Q10 and melatonin-conjugated[37], application of energy (e.g., NIR-LED), proper diet understood in the etymological sense, etc. the RR can become "residual", so that will not disappear nor will evolve towards the structure.

The principle of the process is the Energy-Information - EI - catalytically nature, according to Manzelli. The level of Vibration-Energy - EV, energy related to energy-information - EI - from the perspective of semiotics biophysics is measured on the level of tissue oxygenation: namely the Lt of reflex. Indeed, stimulating the trigger - points to a biological system, such as the liver, "simultaneously" there is built up a simpatic hypertonicity after a latency dependent on the intensity of the stimulus - related to the intensity of liberation in the biological system of adrenaline and nor-adrenaline - we observe the nonspecific gastric reflection - stomach swells - "simultaneously" to reach the critical level of low energy or low oxygen.

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

The production of EI may be endogenous - it is created endogenously in humans through a transformation of breath in subtle and vital energy, and through mitochondrial activity - or exogenous - through the release of substances like melatonin, the adoption of an appropriate diet, NIR-LED (near infrared light) – which stimulate the mitochondrial respiratory function[38], i.e. oxidative phosphorylation.

The endogenous EI born and is formed in the mitochondria, the power plant of human body. The autopoietic system self-produces EI, by transforming EM - Energy Matter - including food, water and O_2 - which is converted into EV-EI. Endogenously we produce ourselves the EV-EI indirectly with the breath, in the sense that vital energy is a

subtle energy that occurs through breathing (it is not air, it is not breath, but it travels and is created together with it).

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

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

In biological systems the EI is transmitted through the classic routes in the local reality, using substrates that reach the target tissue via blood, lymphatic, venous (hormones, cytokines, etc.) or through the nerve pathways (neurotransmitters) characterized by polarization - depolarization: there is time and energy consumption (if I move a substance from A to B, there is energy and time). On the contrary, in non-local reality pure and catalytic EI acts according to what is known in the microscopic world, expression of entanglement, observable with the semiotics biophysics, of both worlds. DNA, like an antenna, simultaneously to "intense" stimulation on certain trigger - points, begins to "vibrate" catalyzing the reactions without energy expenditure, between the compound A and B, with production of C! For example: abdominal lateral pinch of fat "simultaneously" active function of liver PPAR (the mill that burns fat and glucose) revealed by the "simultaneous" local microcirculatory activation[39].

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

In accordance to angiobiopathy, improving mitochondrial activity in the parenchyma and in microvessel cells is involved favorably intracellular free energy and are improved various biological activities: the microcirculation will be normalized. QBS allows accurate and direct study of being and functioning of microvessels and only indirectly of the related parenchyma[40]. If it improves the way of being and functioning of the microcirculation it does mean that it is also improved the way of being and functioning of its parenchyma. This is done by stimulating the activity of mitochondria by acting on the vehicles that transmit EI: metabolism (chemical process), peptides' net (electric-electronic process), but also improving, normalizing tissue oxygenation, expression of the normal operation of mitochondrial oxidative phosphorylation. Indeed, the mitochondrial functional cytopathy is the "sine qua non" of more frequent and severe human disease and not.

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

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

Fractal Dimension fD	**Equilibria**	**State of health**
fD = 1	fix point	chronicity – chronic and acute pathology
1 < fD < 1.9	limit cycle tending to fix point	pathology – tendency to chronicty State of variable severity of disease evolution
1.9 ≤ fD < 3	limit cycle	initial implementation of the tendency to disease /potential pathology- i.e. inherited Real Risk of diabetes– 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 3. fD and equilibria in biological systems

Table 3 shows as fD is a suitable marker to reveal the health of biological system. Followed this approach, deterministic chaos appears to be a source of healthy life. If chaos is not (or is missing) we should create the conditions for it emerges again. Chaos in biology is linked to life: whether is missing and at the same time we can not restore it, is the end. For example, through the use of melatonin conjugated, the energy level raises and then EV-EI increase fostering and perpetuating the non-local reality parallel to local reality. If there were only local reality (which denotes a tendency to disease or pathology or potential disease) it would then need to return to a more complex order (chaotic attractor), but only if there is deterministic chaos arising from well-functioning mitochondria.

3. Conclusions

This article highlights the central role of mit-DNA in the process that underlies the degeneration of pancreatic cells. Mitochondrial function in diabetes explains why T2DM is a growing epidemic. Without enough energy, EI - Energy Information - associated with

EV - Vibration Energy - originated by EM - Energy Matter (i.e., glucose, amino-acids, fats, etc.), the cell can not perform its normal functions. Under these conditions, therefore, the diseases arise under the action of the many negative environmental and acquired risk factors, which are not, however, to define the causes of diseases such as diabetes and cancer, since merely facilitators only for those at risk! In fact, in absence of Inherited Real Risk of diabetes, based on CAEMH mitochondrial cytopathy, all factors achieved are innocent bystanders (Stagnaro, 2009b).

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

For this purpose, the new discipline of chaos theory with its invariant statistic measures, such as entropy and fractal dimension, plays a key role, both from theoretical and practical point of view. Today, the deterministic chaos emerges everywhere: in quantum physics, chemistry, biology, genetics, neuroscience, cognitive psychology, economics, art, cryptography, meteorology, even in the stock exchange.

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

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

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

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

An example of this with incontrovertible evidence of the presence of deterministic chaos in the human body is given by clinical microangiology[41], where the universal constant of Feigenbaum (mark of chaos, comparable in importance to the Greek pi, the golden section and the number e of Euler) always emerges as a relationship between Lt and fD - fractal dimension[42] (i.e., gastric aspecific reflex) in healthy subjects, while in the disease this measure disappears.

This article is a hymn to life and celebrates the extraordinary work of Stagnaro, who like Poincaré and Lorenz, can not even begin to imagine today what will happen in the wake of the immeasurable quality of this initial condition: the chaos as the life is inherently unpredictable, full of beauty, harmony and charm. The deterministic chaos is linked to life! If all this were to fail, as when the sublime energy of love tends to fade, we

would inevitably encounter different equlibria of lower order – pathologies, diseases, chronic or heat death, in biology.

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Endnote

[1] NHS stands for National Health Service

[2] Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose, typically after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagon which acts in the opposite manner to insulin. Glucose thus forcibly produced from internal liver cell stores (as glycogen) re-enters the bloodstream; muscle cells lack the necessary export mechanism. Normally liver cells do this when the level of insulin is low (which normally correlates with low levels of blood glucose). Higher insulin levels increase some anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase). If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not have its usual effect so that glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. When the glucose concentration in the blood is raised beyond its renal threshold (about 10 mmol/L, although this may be altered in certain conditions, such as pregnancy), re-absorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits re-absorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst.

[3] Metabolic syndrome, classic and "variant" – is a term used to define a patient with 3 or more of 5 risk factors:

1) abdominal obesity and waist circumference for men greater than 102 cm or 40 inches, and for women greater than 88 cm or 35 inches;
2) elevated triglycerides, defined as equal to or greater than 150 mg/dL;
3) low HDL cholesterol. Overall for the Adult Treatment Panel (ATP)-III guidelines, low HDL cholesterol is defined as under 40 mg/dL; previously it was under 35

mg/dL (for the purposes of the metabolic syndrome, there are different values for men and women: less than 40 mg/dL; for men and less than 50 mg/dL for women);

4) elevated blood pressure, defined according to lower values than those usually used to define hypertension: systolic over 130 mmHg or diastolic over 85 mmHg.;

5) fasting glucose equal to or greater than 110 mg/dL.

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

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

[6] The Royal Society, London, 1986

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

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

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

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

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

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

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

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

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

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

[17] Metabolic syndrome is a combination of medical disorders that increase the risk of developing cardiovascular disease and diabetes. It is also known as metabolic syndrome X, syndrome X, insulin resistance syndrome, Reaven's syndrome. The pre-metabolic syndrome, as defined by Stagnaro, is the syndrome that precedes the metabolic one, and is linked with congenital real risks and their associated biophysical semiotics constitutions.

[18] Biophysical semeiotic constitutions, detectable since birth, are the inherited congenital ground or terrain of well defined potential diseases clinically hidden, which can last several years before appearing, in the slow transformation process from potential (pre-metabolic syndrome, pre-clinical stages) to effective pathology (metabolic syndrome)

[19] See www.semeioticabiofisica.it , Practical Application, Pancreatic Amyloid deposit

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

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

[22] See Glossary in http://www.semeioticabiofisica.it

[23] See technical pages in http://www.semeioticabiofisica.it – English version

[24] The *synergetic* enables us to study the relation between microscopic level and the macroscopic one, with the principle of "self-organization". This is possible exclusively if, at microscopic level, complex system can modify in qualitative manner; let's think about the fluids in Bènard's cells and the laser. Technically speaking, we define "order parameters" macroscopic observables, which describe the macroscopic behaviour of a system, and "enslavement principle" the behaviour of microscopic elements, according to which it becomes defined when originate "macroscopic observables".
The laser gives us the best example, which illustrates the general rule: the casual emission of waves, under a defined current supply, becomes coherent; when it is exceeded, however, the emission moves toward a deterministic chaotic behaviour. The synergetic, therefore, studies the characteristics of "complex" systems, without considering the nature of their elements, outlining strict analogies between the macroscopic behaviour of the complex systems in spite of the fact that they are really different.

[25] In all tissues, a part from their local different architecture, microvessel diameter oscillates rhythmically during time. The term *vasomotility* refers to small arteries and arterioles sphygnicity, according to Hammersen, and *vasomotion* is the subsequent oscillation of capillaries and post-capillaries venules diameter.

[26] Book in progress. See http://www.semeioticabiofisica.it/microangiologia/common_eng.htm

[27] It is called ascending line because the reflex'intensity is growing for few seconds.

[28] It is called plateau line because reflex'intensity is steady for few seconds.

[29] Microvessels with diameter of 100 μ show a motor activity of 2-3 circles/min. and diameter oscillation intensity of 10-20%. As far as vascular diameter lowers, motor activity progressively becomes more intense and rapid; in terminal arterioles, the frequency is 10-20 circles/min. and the width can reach 100% of mean diameter, causing periodically opening and closure of the microvessel.

This rhythmic activity is mainly spontaneous and direct consequence of periodic contraction of smooth muscle cells of arterioles with 20-90 μ of diameter. Diameter oscillations of small vessels is due to the properties of smooth muscle sells, which have a labile membrane potential and, then, depolarize periodically.
Smooth muscle cells activation by well-known polarization-depolarization processes, which bring about periodic vasoconstrictions, is caused by nervous, hormonal, local biochemical stimuli and also by myogenic stimuli, characteristic of myocells. These stimuli provoke in smooth muscle cells of small arteries and arterioles, according to Hammersen, the onset of depolarization and consequent ionic fluxes and, then, intracellular storage of Ca^{++}, partially due to release from cytoplasmic and membranous storages, which bring about the phosphorylation of myosin, that in turn interact with actine, to start contraction mechanism in presence of phosphorylated nucleotides with high caloric content, produced in mitochondria.
The "vasomotion" varies in relation to temperature fluctuation, O_2 concentration, pH variations, ionic concentration of vascular wall. In fact, it has been demonstrated that Ca^{++} and K^+ fluxes, due to channels voltage-dependent and, respectively, voltage and calcium dependent, at the base of the periodicity of these transports, brings about the rhythm of arteriolar contractions, ruled also by transmural pressure (Gonzalez-Fernandez J.M., Ermentrout B. On the origin and dynamics of the vasomotion of small arteries. Mathematical Biosciences. 119, 127-167,1994).

[30] Small arteries and arterioles as well as capillaries and venules oscillate maximally: in healthy, upper urethral reflex and, respectively, the lower one fluctuate 6 time per minute with "maximal" intensity, 1,5 cm., lasting the highest opening, 7-8 sec.(NN "basal" value = 6 sec.).

[31] Likely, typical *vasomotion* behaviour of dissociated activation, type II, pathological, represents a *defence* mechanism against increased endocapillary pressure. In other words, one may suggest the hypothesis that the lowered *vasomotion*, secondary to blood increased supply (*increased vasomotility*) to capillary net or *microcirculatory misdistribution*, could be caused by a less elastic, more tonic state, with subsequent functional damage of endothelial as well as myocellular mitochondria of EBD and of local microvascular wall, including local periangium, under these circumstances oedematous. As a matter of fact, the described microcirculatory situation ends into interstitial obstruction, first, and subsequently into basal membrane thickening of capillaries themselves. From the above remarks, it does exist a strict relation between "vasomotion" and EBD behaviour, under physiological and pathological conditions, and the abnormalities of EBD is counterbalanced, for months or years, by the increase only of vasomotility, which aims to preserve a physiologic *vasomotion* (dissociation); this fact explains the importance of such structures as regards the regulation of microcirculatory blood-flow, corroborated *clinically* for the first time.

[32] For further information about practical application and all components significances, See: www.semeioticabiofisica.it/semeioticabiofisica/applicazioni.htm

[33] Figure 1 shows as to listen to vagal type aspecific gastric reflex: in the stomach both fundus and body are dilated, while antral pyloric region appears contracted. Arrows show lines upon which digital percussion must be applied, directly and gently, on the skin, moving from outer side in direction to the belt piece of stethoscope. When digital percussion is applied directly on stomach projection area, sound is perceived more clear and intense and "it seems to come from a site near to doctor's ears".

[34] See http://www.semeioticabiofisica.it/microangiologia/Documenti/Eng/A Zona Grigia_eng.doc

[35] In the stomach, body and fundus dilate; on the contrary, antral-duodenal region contracts.

[36] H.A.G.R., when pathologically lasting 4 seconds or more (NN < 4 seconds), indicates local microcirculatory remodelling, and thus MFR impairment due to newborn-pathological, type I, subtype b), aspecific, EBD, which reduce tissue oxygenation, through lowering microcirculatory blood-flow.

[37] Melatonin is a natural substance that our body produces itself. It is produced by synthesis in the laboratory and placed in the body is to act on mitochondria, especially increases mitochondrial phosphorylation, it produces more EV and therefore greater EI and this must be for the benefit of the

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

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

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

[40] The micro-circulatory remodeling is directed by the way of living and working on the parenchyma: if the subject is healthy, is healthy the related parenchyma on the microcirculation (see angiobiopathy theory, dealing with diseases of blood and lymph vessels in accordance with the semiotics biophysics). Certainly a loss, rheumatism, immune, infectious, can act both directly and indirectly.

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

[41] See http://www.semeioticabiofisica.it/microangiologia/common.htm

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