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hronic liver disease invariably leads to excessive and disordered deposition of collagen resulting in the irreversible end point of cirrhosis, which is still one of the most common causes of death worldwide. Thus, prevention or suppression of fibrotic changes in the liver are of crucial importance. In such peculiar set up, fibrosis is not a simple deposition of excess matrix in liver tissue as this phenomenon is associated with a change in the type of matrix molecules (including collagens, glycoproteins and proteoglycans) and histological redistribution of the matrices. Although a number of potential inhibitors of hepatic fibrosis, such as steroids, interferon γ, colchicine and 16,16-dimethyl prostaglandin E₂ have yielded beneficial effects in experimental settings, none of them has been successfully used for the treatment of patients while posing a number of severe limitations in clinical use. It is estimated by the World Health Organization that the global prevalence of hepatitis C virus (HCV) infection averages 3%, representing nearly 170 million HCV infected persons worldwide and with an annual mortality per 10,000 patients between 11.5% in females and 23.5% in males. On the basis of studies among blood donors, anti HCV prevalence varies from very low rates (0.01-0.1%) in United Kingdom and Scandinavia, to lower (0.2-9.5%) in Western Europe, intermediate levels (1-5%) in Eastern Europe, Mediterranean and Mideast or very high rates in Egypt (up to 25%). A number of ethnic differences, lifestyle and behavioral attitudes are known to affect exposure rates. For instance, from the epidemiological profile point of view, Japan and Italy share the so-called "second pattern" where the age-specific prevalence is low in children and younger adults but increases sharply among older persons who account for most infection, reflecting a higher risk for HCV infection in the past (30-50 years back). Whereas in Saudi Arabia, where there is a varying seroprevalence ranging from 0.99-5%; the burden of HCV infection is expected to increase in subjects entering their fifth and sixth decade, as reported in a dedicated and exhaustive issue of a major Middle-East medical journal edited by Prof. Shobokshi. The main anatomic pathological feature of liver cirrhosis is the progressive formation of fibrous tissue leading to an overall organ disarray and functional failure. This explains the constant incidence of hepatocellular carcinoma which occurs as an unavoidable event in the natural course of long standing chronic liver disease at a rate of 10/10,000. The complication of liver cirrhosis (esophageal varices, hypersplenism with decreased platelet count, ascites and so forth) are mainly dependent upon portal hypertension which, on its turn, is the consequence of diffuse parenchymal fibrosis and nonfunctioning regenerative nodules. Despite the therapeutic armamentarium has been enriched by new effective antiviral drugs and regimens in the last years, there is a substantial percentage of nonresponders for whom cirrhotic transformation leads to death.
cannot be substantially prevented. Moreover, patients with established cirrhosis are not feasible for antiviral treatment and therapeutic achievement as only in the last decades have improved the treatment of related complications but also being unable to substantially modify the natural history of the disease. In particular, despite several promising experimental data, there is no validated pharmacological treatment to reduce liver fibrosis which is only an epiphenomenon of the disease but with relevant pathogenetic implications. As a matter of fact, a review of authoritative large scale studies in which a combined antiviral regimen had been rationally prescribed to non cirrhotic patients with HCV related chronic hepatitis shows only a 20% improvement of fibrosis and in the most feasible group of sustained responders. This to point out that even in the early stages of the disease and with an effective suppression of the viral replication, once activated fibrosis seems to keep following detrimental pathophysiological mechanisms which are still to be fully elucidated. Such series of events might be interpreted from a biophysical viewpoint. In the occurrence of tissue damage due to diseases or trauma a consequent and concomitant healing process takes place and this might be reparative (scarring) or regenerative, only the latter allowing a complete functional recovery. Liver cirrhosis as well as other relevant chronic diseases brings a functional impairment of the damaged tissue as a consequence of a progressive inability to sustain a regenerative process which is overcome by scarring phenomena. Such unavoidable sequelae is not organ specific, little or no related to the pathological noxae but, as an epiphenomenon, can be found in virtually all chronic-degenerative diseases, in aging and in several mechanical trauma within what seems to be a failure of the overall regenerative dynamics. Given the inner regenerative ability of every tissue, the lack of it with time or following diseases implies the occurrence of a general factor which is common to many diseases irrespective of their pathogenesis but all invariably facing, although with different time lag, the same reparative versus regenerative phenomena. In order to better figure out the research supporting such novel modality of understanding and treating biological phenomena one has to appreciate by the morphological abnormality of the system which leads to phenomena ranging from sub clinical to very widespread damage. Function itself is, thus, also varies being energy-dependent itself. From a thermodynamic point of view, the cell is an open system as it continuously exchange matter and energy with the surrounding environment. Although, such factors seem constant as for their concentration and spatial disposition, it is indeed a dynamic equilibrium between continuous degradation and synthesis of molecules. Cells have the characteristic to evolve towards a more complex organization, like, differentiation, and during such event the system shifts from a "probable state" to a less probable state as it decreases its entropy at the expenses of energy. Accordingly, at higher complexity level we can verify that form and function of an organ are strictly linked with utilizable energy so to maintain an ordered state. A cirrhotic process is mainly characterized by a significant abnormality of the morphology, such as, by a structural disorder (increased entropy) which is also but not only, reflected with the formation of scarring tissue leading, through a vicious circle, to a further functional loss. Whenever a chronic inflammatory liver process occurs continuous energy dependent efforts of regeneration take place with a marked depletion of the functional reserve. Thus, the visible morphological abnormality is the result of the rupture of the homeostatic equilibrium as the need of energy to sustain the function exceeds the available energy and that one provided by functional reserve. In the case of a chronic viral hepatitis where the functional reserve is constantly under siege, the overall system is slowly but irreversibly transformed into a thermodynamically more "probable state", that is, of higher disorder where reparative processes (disordered) overcome the regenerative ones (ordered). Cirrhosis is the unavoidable consequence. Thus, it is important to redefine the biological link between form and function.

Form. Maintained at the expenses of utilizable energy which, in accordance with thermodynamic laws, inevitably decreases with time given the same chemical energy introduced. Entropy represents that part of energy within the system which cannot be converted into work any longer and its entity increases during each energy transformation. In other words, the entropy of a system represents the degree of disorder of the system itself which is appreciable by the morphological abnormality of the given organ or tissue. Such events are primarily the regular result of normal ageing processes but also due to the relentless activation/rapid depletion of the functional reserve in the case of chronic disease or from very widespread damage.

Function. This is also an energy dependent process closely linked to form, the alteration of which leads to phenomena ranging from sub clinical to clinical in nature, depending on the severity of the morphological damage. Function itself is, thus,
linked to the entropy of the tissue/organ/body, which represents an indirect measure of the latter’s efficiency (the greater the entropy, the lower the function, the greater the structural disorder). It follows that if a variation of negative entropy can actually be introduced by a positive modification from the external energy variable (an event that is possible as we are dealing with a thermodynamically open system), it is to be expected that a counter process that is inverse of the one causing the morpho-functional reparative modification (such as, scarring, fibrotic change), namely, a regenerative tissutal event. This occurrence would simply mean a substantial increase of the dynamic capacity of the functional reserve, given that the genetic information remains unaltered. Under normal conditions entropy is lowered at the expenses of the energy produced by the oxidation of nutritional substrates. Such energy is only partly converted into chemical energy and stored within molecules such as adenosine triphosphate and creatinphosphate. Moreover, further loss of energy takes place during its transformation to maintain homeostatic processes while over 50% of the energy introduced with food is used to produce and maintain body temperature. Thus, to further decrease body entropy it is necessary not just to discharge electromagnetic energy but to deliver and modulate a form of energy which would have to be "compatible", namely, feasible to produce work for the maintenance of cellular homeostasis but with a more efficient conversion rate when compared to that one provided by food intake.

A theoretical possibility would be by delivering to the biological system a form of energy devoid of matter (electromagnetic) with specific characteristics (emission spectrum, power, information content, reduced dispersion during the transfer of energy to heat) so to be recognized by the organism comparably with that one generated by the usual chemical transformation processes. Such phenomenon takes place in plants rich in specific chlorophylls receptors which are able to capture and convert the electromagnetic spectrum generated by the sun. Although human being lack such receptor, it is possible, under previously mentioned conditions, to convey sequences of electromagnetic fields by induction, namely, using the resonance characteristics of cellular systems. Recognition by the body of the energy as "self", such as a synthetic analog of biological energy, is one of the keys of the successful interaction with the target organ achieved by this new modality and the lack of such feature would otherwise exert damaging effect as it is used in some therapeutic devices (laser, linear accelerators and so forth) which operates under totally different principles.

Such technology, named as Delta-S entropy variation system, has already been certified for hospital and outpatients use in Italy. It uses non-ionizing electromagnetic fields of very low power (<3 v/m) which are dynamically modulated by an "export system" which tailor its required characteristics of compatibility and organ selectivity so to lower entropy level. There are no literature reports regarding possible harm to human health (particularly at such low power ratings) in the short waves - very high frequency region (International Committee Non-Ionizing Radiation Project by World Health Organization guidelines on non-ionizing radiations), although the entire spectrum lying between these 2 bands has for decades been saturated by radio transmitting equipment operating at very high power (even thousands of times greater than those used in the system).

The clearest way to verify whether this is what really happens is to observe the conversion of this ‘synthetic’ energy into work available to the biological system where such restoration of form and function in damaged organs or tissues would otherwise not be possible in normal conditions. While larger studies are awaited, to date there is a preliminary case-study experience in liver cirrhosis, in long-standing dermal scarring lesions and in some clinical aspects of aging which would confirm the clinical applicability of the theoretical model insofar developed.

**Preliminary data in liver cirrhosis.** We studied 6 HCV+ (child A-B) cirrhotics with overt symptomatology and portal hypertension who stopped any medication and underwent daily 40 min sessions of Delta-S DVD, an entropy variation system, for 6 months and followed up monthly. After 6 months, patients showed either a complete (80%) or a partial (20%) regression of fatigue (Fisk score), a complete reversion of depression (Hamilton score), peripheral edema and pruritus. As assessed by independent observers, despite having stopped beta-blockers, F1 varices disappeared (60%) while F2 ones were reduced to F2. Doppler ultrasound aspect of partial (40%) or total (20%) atrophy were either reduced (60%) or reverted to normal (20%) while overt scarring nodules disappeared in 40%. Portal vein respiratory dynamics improved (80%) or normalized (20%). A significant increase of active B lymphocytes and natural killer cells (mean increase was +71.2% p<0.002) also occurred. Although limited, such preliminary data suggest that this novel biophysical technique can positively affect "biologically-irreversible" parameters, thus, representing a promising new modality to effectively treat liver cirrhosis.10

Cutaneous keloids and post-burn/trauma scarring 12 patients presenting scar tissue due to traumas or
burns were treated (40 sessions using a series “ETV Delta-S” Entropy Variation System). The lesions initially displayed keloid features, with traction on the underlying tissues and consequent retraction and loss of elasticity of the cutaneous layers, lymphoedema of the surrounding tissue associated with alteration of normal skin pigmentation to a reddish-violet color. At the end of treatment the scar tissue displayed greater elasticity, reduced cutaneous retraction and a consequent enhanced mobility of the underlying cutaneous layers, normalization of lymphatic circulation and lastly an improved pigmentation of the lesion. No side effects were observed either during treatment or in the subsequent monitoring period.11

Future perspectives (aging processes). Using a slightly modified device (Delta-S electroventriculography) a number of future projects aimed to treat physiological aging are under way. Some preliminary positive experiences in treating age-related immunological, respiratory, muscular, cardiovascular and microcirculatory decay together with diabetic foot syndrome12-14 have prompted a further advancement of the studies on a larger and more homogeneous study population.

The preliminary data obtained by introducing non invasive entropy variation techniques having no side effects opens up a new multidisciplinary approach to medical problems, in which an extensive use is made of theoretical tools capable of rationalizing certain basic research procedures. From a practical clinical point of view, it may be claimed on the other hand that these pilot studies seems to indicate the direction to be followed in order to make a contribution to substantially increasing the quality of life of patients15,16 that cannot easily be treated using other methods.

References