Insomina is a Sign of Di Bella's Oncological Terrain.

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Introduction.

Living organisms have notoriously evolved internal timekeeping mechanisms to synchronize behaviour and physiology with the cycles of day and night. These biological clocks have been found in a lot of organisms, as fungi, fruit flies, hamsters, and humans. The biological clock of humans is found in the brain. There is a general agreement that in such event an important role is plaid by the path of light input to the suprachiasmatic nucleus (SCN), a collection of neurons that regulates our circadian rhythms. The SCN contains several cell types and several different peptides (including melatonin, somatostatin, vasopressin and vasoactive intestinal peptide) and neurotransmitters, and it interacts with many other regions of the brain, especially epihysis.

In a fascinating article, Authors have demonstrated that the hormone melatonin phase shifts circadian rhythms generated by the mammalian biological clock, the hypothalamic suprachiasmatic nucleus (SCN), through activation of G protein-coupled MT_2 melatonin receptors (1). The pretreatment with physiological concentrations of melatonin in rat decreased the number of MT_2 melatonin receptors expressed in mammalian cells in a time and concentration-dependent manner. Furthermore, MT_2 melatonin receptors were internalized upon pretreatment with both physiological and supraphysiological concentrations of melatonin (1). In rats, the recovery process was partially protein synthesis dependent. Furthermore, exposure to physiological concentrations of melatonin for a time mimicking the nocturnal surge (8 h) desensitized functional responses mediated through melatonin activation of endogenous MT_2 receptors (1).
The authors conclude that in vivo the nightly secretion of melatonin desensitizes endogenous MT_2 melatonin receptors in the mammalian SCN, thereby providing a temporally integrated profile of sensitivity of the mammalian biological clock to a melatonin signal (1).

The Human Suprachiasmatic Nucleus

In mammals, the controlling clock component that generates a 24-hour rhythm is the suprachiasmatic nucleus (SCN), located in the hypothalamus. The SCN produces a signal that can keep the rest of the body on an approximately 24-hour schedule, but in individuals negative for Di Bella's Oncological Terrain (2-10), as I am going to demonstrate for the first time in this article.
Even in the absence of external time cues, humans maintain a sleep-wake rhythm very close to 24 hours. Typically an organism's circadian system is made up of components that receive environmental input, that generate the 24-hour rhythm, and that mediate rhythmic output to all the tissues of the body. In mammals, the controlling clock component that generates a 24-hour rhythm is the suprachiasmatic nucleus (SCN), located in the hypothalamus. SCN signal can keep the rest of the body on an approximately 24-hour schedule.
However, because the internal clock's period is not exactly 24 hours, environmental cues—most importantly, light—are required to reset the clock each morning and keep the organism synchronous with the external world. Notoriously sunlight represents a signal that can reset neurons in the SCN.

At the moment, Authors agree with the statement that light enters the eye activating neurons in the retina, and converting photons to electrical signals. The retinal neurons transmit the electrical signals from the retina via long axons in the optic nerve. Along the way is the optic chiasm, where the optic nerves from the left and right eye meet and cross. At the optic chiasm, visual information continues toward the back of the brain, where it is processed into images that we can consciously

perceive. The neurons carrying information to the SCN, however, take a different path. They exit the optic chiasm and turn upward, toward the SCN, so called because it is located above the chiasm.

However, with the aid of Quantum Biophysical Semeiotics (See my website www.semeioticabiofisica.it and www.sisbq.org), I have demonstrated that in biological systems, beside local realm, weherin transmission happens by losing time and energy, as above described, according to classic physics, there is also no-localm realm, characterized jet by a four dimensional space/time, but showing 2 T/D and 2 S/D: the information is "simultaneous" in the space and synchronous in the time, whitout losing energy since its mechanism nature is cathalitic,according to quantum biophysics (11-21).

The SCN is a small, paired, wing-shaped structure, located at the base of the brain, exactly in the hypothalamus. Within each side of the SCN is a network of up to several thousand neurons, normally synchronized with the activity of its neighbours.

Inside a single SCN neuron, the protein product of a biological clock gene turns off production of more protein, forming a negative feedback loop. Even in the absence of external time cues, humans maintain a sleep-wake rhythm very close to 24 hours. Typically an organism's circadian system is made up of components that receive environmental input, that generate the 24-hour rhythm, and that mediate rhythmic output to all the tissues of the body.

The SCN produces a signal that can keep the rest of the body on an approximately 24-hour schedule, as above refered. However, because the internal clock's period is not exactly 24 hours, environmental cues—most importantly, light—are required to reset the clock each morning and keep the organism synchronous with the external world, by regulating tissue level of melatonin.

Light enters the eye and activates neurons in the retina that convert photons to electrical signals, but especially in the first phase, according to Quantum Biophysical Semeiotics, through "simultaneous" information of some occipital brain regions, as demonstrates the following clinical evidence.
When an healthy individual opens his (her) until before closed eyes, brain occipital circonvolutions show "simultaneously" microcirculatory activation, according to type I, associated, physiological (3, 22-25).
Further information reader may find in the websites http://www.semeioticabiofisica.it/microangiologia/, and www.sisbq.org.

Unfortunately, regarding retinal in-put transmission to the brain, physicians all around the world continue to think erroneously that the unique way of energy transmission is the retinal neurons transmission of the electrical signals from the retina via long axons in the optic nerve. Along the way is the optic chiasm, where the optic nerves from the left and right eye meet and cross. At the optic chiasm, visual information should contune toward the back of the brain, where it is processed into images that we can consciously perceive, losing time and energy. The neurons carrying information to the SCN, however, take a different path. They exit the optic chiasm and turn upward, toward the SCN, i.e., above the chiasm. All that happens really in the second phase of visual perception.

In a few words, such as transmission is firstly "simultaneous", according to non local realm of biological systems, I have demonstrated in earlier articles (11-21), and secondly it happens as generally admitted, losing time and energy (13,19,20).

Role of hormones and neurotransmitters in SCN functioning.

A major function of the SCN in mammals is thought to be to generate biological rhythms with a period of about 24 hours, and these circadian rhythms are normally related to the light-dark cycle. They underly daily rhythms of activity and of hormone secretion. The involvement of the SCN was first shown by experiments in which damage to the SCN in animals resulted in abnormal activity rhythms.
In all mammals many physiological processes are governed by circadian rhythms; for example the secretion of many hormones, such as melatonin, follows a 24-hour cycle.

Specialized neurons in the ventrolateral SCN have the ability for light-induced gene expression. If light is turned on at night, a singular componen of SCN relays this information throughout the entire SCN, as demonstrates clinical evidence: in a few second, local microcirculatory activation disappears, followed by basal microvessel fluctuations (3-5, 26)

The SCN receives notoriously information via the optic nerve. However, neurons in the dorsomedial SCN can generate a 24-hour rhythm of activity that can persist even in constant darkness. The SCN sends information to other hypothalamic nuclei and the pineal gland to modulate body temperature and the production of hormones such as cortisol and melatonin.
The SCN is one of four nuclei in the brain that receive nerve signals directly from the retina, the other three are the lateral geniculate nucleus (LGN), the superior colliculus, and the pretectum.
The LGN passes information about color, contrast, shape, and movement on to the visual cortex and itself signals to the SCN. The superior colliculus controls the movement and orientation of the eyeball. The pretectum controls the size of the pupil.

However a key feature of a true circadian pacemaker, such as the SCN, is that it can produce rhythms with an approximate period of 24 hours even in the absence of any change in light. True circadian rhythms thus persist when animals are maintained in constant light or constant dark. Thus light cues do not themselves determine the rhythm, they just entrain the rhythm, keeping it locked to the light-dark cycle.

Insomnia and wakefulness are related to other important disorder, including Di Bella's Oncological Terrain.

Epidemiologic studies indicate that disturbances in sleep and wakefulness predict the presence of current, and the emergence of future, psychiatric impairments, including depressive, anxiety, and substance use disorders (27).
At the end of the life cycle, a predictive value for disturbed sleep was demonstrated for individuals above the age of 55 by Authors (28) who presented data from 140 patients suffering from major depression disorder (MDD) consecutively visiting in a family practice setting over the course of 6 months and 140 controls, matched with respect to age and sex.
In these aged patients, improvement in mood was correlated with increased sleep quality in both depressed and nondepressed patients. However, other lifestyle indicators were not.
Young and colleagues added to the database supporting the predictive value of insomnia in psychiatric morbidity in a cross-sectional study of 49 older adults (ages 50-89) with bipolar disorder; 60% reported a history of suicidal ideation (29). Positive correlates for suicidal ideation included white race, prominent sleep difficulties in the depressed phase, and younger age.
Taken togheter, these data extend the predictive value of disturbed sleep in the psychiatric disorders to younger and older age spectra, obviously only in those individuals involved by Constitutiond-Dependent Inherited Real Risks (3, 4, 48).

For the first time, based on a sufficiently long, well established, clinical experience, I emphasise suprachiasmatic nucleus disturbances, evaluated with Quantum Biophysical Terrain, as a typical sign of Di Bella's Oncolgocal Terrain.
As a matter of fact, among the principal neurotransmitters involved in conveying photic information to the SCN have been identified glutamate, and PACAP. Light stimulation of the retina results in direct secretion of glutamate from the Rethino Hypothalamic Tract (RHT) into the ventral VIP-containing part of the SCN (30, 31). Glutamate as a transmitter at RHT/SCN synaptic connections plays an important and critical role in mediating photic regulation of circadian rhythmicity. RHT terminals innervating the SCN show glutamate immunoreactivity associated with synaptic vesicles which confirms the role of glutamate as a neurotransmitter (32,33).
Different types of glutamate receptors were identified and localized in the SCN using in situ hybridization and immunocytochemistry (35).

My principal interest here is to underly the central role plaid in SCN disturbaces by melatonin as well as somatostatin, two paramount components of Di Bella's Oncological Terrain, *conditio sine qua non of* cancer onset in SCN in bith function and disturbances (2-4,10,22).

Melatonin, the so-called darkness hormone, proved to be of great importance in the functioning of the SCN, as demonstrate the following experimental evidence: "symultaneously" to eye closure, physician observes microvessel activation of epyphysis and after one sec., also the activation of SNC microcirculation, according to type I, associated (2-4, 22).
In my clinical researches, among the most important target of melatonin in humans, there is the SCN, as it contains the highest density for melatonin receptors (4, 10, 22, 36).
A double effect of melatonin in the SCN, namely, an immediate effect and long term effect, has encouraged its worldwide use against the ill effects of jet lag. Acceleration of sleep initiation in humans at circadian phases when the SCN would normally stimulate waking is another reported action of melatonin (37).
In terms of long term effect, melatonin can phase shift and amplify circadian rhythmicity of the SCN. Melatonin application has been found to be useful in synchronizing the endogenous circadian rhythms not only in people who suffer from jet lag, but also in blind individuals, patients with dementia, and shift workers (38).

In spite of the experimental evidence favouring a very important role for melatonin in the circadian timing system, the exact role of melatonin has not been demonstrated clearly. Melatonin and seasonal rhythms are intimately related in mammals, and this has been well documented (37-40). The retinohypothalamic-pineal (RHP) axis is comparable in animals and humans. In both animals and humans melatonin is secreted exclusively at night. The RHP is capable of detecting changes in night length to make proper adjustments for the duration of nocturnal melatonin secretion so that animals can use this melatonin message to trigger seasonal changes in behaviour (41).
I have demonstrated the central role of Melatonin in the pathogenesis of Di Bella's Oncological Terrain (2-4, 22, 23).

A second neurotransmitter lowered typically in Di Bella's Oncological Terrain is somatostatin (SST). SST producing neurons of the SCN are located in both the core and shell portions and form a distinct peptidergic neuronal group. The shell portion of the SCN, which is likely to be involved in the regulation of overt rhythms, projects within the SCN through SST fibres. Aging effects of SCN neuropeptide expression, like the circadian profile of peptide expression, may be species specific as far as the SCN is concerned. Synapse of SS fibres on VIP and AVP neurons and presence of SST receptors in the SCN is suggestive of a regulatory role for SST on other peptidergic neurons. An inhibitory modulating role of SST on VIP rhythmicity has been demonstrated (42). Increase in SST immunoreactivity could explain the observed VIP decrease with

aging, and, if enhanced SST immunoreactivity reflects a release deficit, this may lead to reduction in inhibitory action.
One must remember that VIP, a gut polypeptide, has been identified as one of the main neurotransmitters of SCN neurons and participates in SCN function. In addition, VIP signalling through its receptor serves two important functions in the SCN, namely, circadian rhythmicity in a subset of neurons and maintenance of synchrony between intrinsically rhythmic neurons. This may also mean that VIP-expressing neurons themselves are circadian pacemakers in the SCN for establishing and synchronizing rhythmic activity (42).
From the above remarks, I am allows to state that in individuals involved by Di Bella's Oncological Terrain, characterized by lowering of both melatonin and SST, the first plays the central role in SCN disturbances.

Regarding the link between neurotransmitters and some human disorders, researchers have started to identify the role of the SCN in a lot of disease conditions. SCN dysfunction, particularly in terms of neurotransmitter content, has been associated with several chronic diseases such as hypertension, diabetes, and depression (43, 44).
An awful number of observations strongly suggest that a changed SCN may precede the development of hypertension. There is also evidence that circadian disturbances may be detected prior to the development of diabetes or hypertension (45, 46) Further evidence that the functionality of the biological clock may be affected in humans by diseases such as depression and hypertension has been provided by numerous Authors.

According to my clinical experience, all researches are fundamentally biased, since the majority of Authors ignore Quantum Biophysical Semeiotic Constitution (45).
A 55 year-long clinical experience allows me to state that the Authors, overlooking these predispositions to related disorders, cannot correlate neurotransmitters alterations with a lot of disorders, like SNC dysfunction and psychiatric diseases, hypertension, and diabetes.
In fact, these disorders can occur exclusively in presence of the related Quantum Biophysical Constitutions (2-8, 23-25, 48).
In the course of efficacious therapy, e.g., with selective serotonin reuptake inhibitors, both neuronal and cerebral evoked potentials, now-a-days assessed at the bed- side with the aid of Quantum Biophysical Semeiotics in reliable way, have to ameliorate clearly (49, 50).
In addition, under identical condition, cerebral microcirculatory functional reserve improves statistically (2-8, 10, 23-25), when bedside assessed with the aid of SPBM, i.e. "Single Patient Based Medicine" (24, 48, 49).

Melatonin Deficiency: the Link between Insonnia, Night Shift and Cancer.

In a large literature, the link between night shift, insomnia and cancer are largely described, although till now Authors mainly ignore the existence of Di Bella's Oncological Terrain, I suggested since a decade as a the *condition sine qua non* of malignancy (2-10).
In 2001, in a large, and interesting prospective cohort study of shift-work and breast cancer, the risk of breast cancer was statistically significantly elevated in postmenopausal women who worked for 30 or more years on rotating night shifts, compared with those who never worked at night. (51)
A few years later, in 2009, it was reported that women in Denmark, who developed breast cancer after many years of working night shifts, received compensation despite only limited research supporting the link. Out of 78 cases notified to the national board of industrial injuries in Denmark, 38 have received compensation through their employers' insurance schemes.

All of the women had worked night shift patterns for at least 20 years and were otherwise at low risk – they had low alcohol consumption and no family history of breast cancer. The Danish decision was based on a ruling by the *International Agency for Research on Cancer* (http://www.iarc.fr/) in December 2007 which stated that "shift-work that involves circadian disruption is probably carcinogenic to humans."
Despite Oncological Terrain was overlooked, other experimental studies have indicated the majority of totally blind people whereby melatonin is never suppressed by light exposure since most totally blind women are not receptive to light, could be protected from cancer through this mechanism.
Richard Stevens, Ph.D., cancer epidemiologist at the *University of Connecticut Health Center*, Farmington, Conn., and colleagues published a study in the *British Journal of Cancer* that found breast cancer risk decreased by degree of visual impairment, from moderate low vision to totally blind. "It was initially thought that blind women might have a greater risk of developing breast cancer because some studies have reported that they have earlier menarche and delayed child-bearing age, both of which have been seen to increase the risk of breast cancer in women," R. Stevens said. "Yet these women have been found to have a lower risk of developing the disease." They concluded that this suggests a dose-response relationship between visible light and breast cancer risk (52).

Conclusion.

The results of my research, emphasising the insomia as another sign of Di Bella's Oncological Terrain, need certainly to be further corroborated on a sufficiently large scale. However, on the base of their concordance, my results allow to state that Melatonin deficiency is the link between insomnia and Di Bella's Oncological Terrain.
As a consequence, in the treatment of insomnia, physicians have to prescribe drugs, as well as physical therapy (e.g., patches emitting energy concordant with biological systems, as epiphysis and SCN), aiming to normalize melatonin tissue level in diencephalic hypothalamic nuclei and epihysis, utilizing therapy able to transform Oncological Terrain into its "residual" variant, which prove to be no dangerous (51).
To insomnia therapy with drugs and physical treatment normalizing melatonin tissue level, I shall dedicate a next paper.

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