Cancer as a Reversible Disease

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Its Real Nature, Spontaneous Regression and Integrative Treatment

By

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To my mother

To my wife

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INTRODUCTION

It has become obvious that the unsatisfactory approach to cancer is due to an insufficient understanding of the basic biological processes of the healthy organism, and to an inadequate comprehension of the native and original "language" of the physiological functions of the body and mind. If this language has not been adequately learned, communication with the living events in the body and soul, in both research and clinical practice, is difficult and sometimes impossible. For this reason, the very first step in the investigation of cancer is the establishment of an upgraded communication with the physiological processes through a better understanding of this language. This language should not emerge exclusively within the framework of any single paradigm. It should be constructed, without any discrimination, by the harmonious coexistence and appropriate integration of existing relevant and valuable paradigms, which can offer the required evidence from research data and/or clinical applications. In any instance, common sense and justification should never be neglected; on the contrary, they should constitute the cornerstone for any final confirmation and acceptance of data.

After satisfactorily learning, understanding and using this language, the pathway of growing children may be followed, where challenging questions are asked on matters and objects, that do not deserve any simple answers from adults, for example "usual" and "normal". The more provocative, original and spontaneous the questions set, the nearer the truth or a "better truth" is the expected answer. The basic prerequisite to getting the right answers is to put the appropriate questions, integrating clear common sense and reasoning and avoiding the traps of dogmas and axioms. Then, the proper methodology demands both statistically based data, forming a solid rational basis and the "extra-ordinary" and "curious" events, that seem to be incidentally moving out of the safe and "normal" framework of statistical analysis; in the last case, great truths and principles may be hidden, that may permit a "scientific revolution" according to epistemology. Such "curious" and "extra-ordinary" events are a continuously growing number of cases of cancer regression, the complete disappearance of any pathological data of cancer without any indicated conventional treatment. These "miraculous cures", assessed along with impressive research data of cancer cells'

reversion to normal phenotypes, open a most promising roadmap for an upgraded and more effective cancer treatment. These most encouraging clinical and research data show that cancer reversion is neither "miraculous" nor random, a matter of chance and luck, but a matter of limiting our current ignorance according to Nicholson, the eminent late Professor of Pathology at Guy's NHS London Hospital, who declared that we first raise dust around us and then complain that we cannot see.

Cancer remains a source of misunderstanding and controversy. There is a vast literature on cancer theories. In this book are descriptions of interesting and promising, whether acknowledged or not, ideas and theories, as they may be approached in the medical literature. Although none of the hypotheses of carcinogenesis elucidates a general scenario applicable to all cases of cancer, they are all, nevertheless, valuable in forming the overall image of cancer generally and its stages specifically.

Cancer has been by far an object of mystery, besides terror and despair. Cancer is the modern "sacred disease", to employ the relevant Hippocratic expression from the renowned treatise on epilepsy, which also frightened people and caused disproportionate terror and panic. Decades of effort after World War II have proved how much more effective cancer treatment can be, based simply on a reductionistic approach to complex phenomena. Even more impressive is the fact that treatment protocols are still based on mechanistic conceptions, while in the last decades developmental biology and systemic physiology have offered a wealth of new well-evidenced knowledge for a more systemic, holistic and integrative cancer treatment. Cancer is still faced and treated as an infectious disease, in which, instead of microbes and viruses, the enemy is exclusively the cancer cells and the only target of the war against cancer is to exterminate them without pity. Though somatic mutation theory was long ago considered inadequate for understanding cancer sufficiently, the current model of conventional cancer therapeutics has been based wholly on it.

The terms "tumor", "neoplasm" and "cancer" are often incorrectly used as synonymous in the literature. Every space-occupying pathological lesion in the organism is a "tumor", which may have a neoplasmatic, inflammatory or restorative nature. A "neoplasm" is a tumor with autonomous growth. When this growth is local, circumscribed, with clear margins and boundaries and the cytologic characteristics do not exceed those of hyperplasia, then this neoplasm is called "benign". When this growth is invasive and potentially metastatic and/or the cytologic characteristics of the neoplasm include specific nuclear aberrations and abnormalities,

basically high-grade dysplasia or anaplasia, then this neoplasm is called "malignant". When a malignant neoplasm obtains the morphology of a tumor, then the tumor is called a "malignant tumor" or "cancer". Certainly, the term "malignant tumor" is suitable, since it is a matter of conception and vision of "cancer" as a local or systemic disease that accordingly dictates the appropriate use of the term. Integrative medicine encourages the conception of cancer as a systemic disease, while holistic medicine recognizes cancer as a systemic disease according to its basic principles.

According to fastidiously collected data on "borderline cancer", the situations of abnormal tissue patterns, which may or may not indicate cancer, are not at all few (Park, 1980). Although, established studies indicate in statistical terms which tumors may be regarded more or less malignant, they are not sufficiently accurate in predicting the course and outcome of any individual cancer case (Blanco, 1977). Though cancer is a systemic disorder, albeit usually with a dominant local expression, the treatment of cancer has been mainly based on a simple mechanistic concept: if all cancer cells are removed or destroyed, a cure will result, otherwise if any cancer cells remain alive, recurrence and/or metastasis is inevitable (Park, 1980). The behavior of a cancer of any individual type may be far from "standard"; the crucial element is the inherent biological variability of the individual lesion and case, which is the "incomplete factor in cancer prognosis" (Gordon-Taylor, 1959).

The purpose of the book is to first present a reliable integrative vision of cancer, as this may emerge from a fastidious, well targeted and planned review of quite a lot of interesting relevant views, images, theories, research data and clinical applications. This review has to be objective and unprejudiced and the collected data have to be studied according to the scientific method, knowledge and practice and, also, according to common sense, especially when facts dictate it directly and obviously. The key factor is the right selection of questions in the search, according to the very wise observation that the right answers come only after the right and well-formulated questions.

I am not a historian, though I have devoted a part of my academic teaching and writing in the history of medicine, which attracted my interest from my youth, to discover valuable pieces of knowledge, in a similar way to archaeological excavations, expeditions, and adventures. I tried to find, collect, assess and assemble such sophisticated pieces by exploring the past and present at the most indicated points, according to the most interesting challenges and mysteries in the "cancer wonderland". I wrote this book on

cancer neither as a historian nor as a philosophist of medicine. I wrote it as a pathologist, with an inherent, specific and constant interest in cancer, as this was promoted and cultivated through my active involvement in integrative medicine. The role of the pathologist deserves a much better understanding. It involves the search, detection, and evaluation of all the data related, directly or indirectly, to the *causa causalis*, that is the one or more causative factors of the disease; the *causa occidentalis*, that is the circumstances and conditions that encouraged, induced, and accelerated the progression of the pathogenetic events; and the factors that evidently seem to influence positively or negatively the promotion or regression of all the expressions of the disease in each individual case. Unfortunately, modern technology limits more and more the personal intervention of the pathologist in cancer and motivates him towards only employing and completing protocols for the clinical fellows. The pathologist can play the traditional, coordinating and surveying role of the discipline of pathology, based not simply on histopathological findings and observations, but on analysis and synthesis of all the data of the whole organism of the cancer patient, after a detailed case-taking according to the principles and practice of modern integrative medicine.

A proper approach, understanding and treatment of a disease first demands a proper approach and understanding of health, and then the causative factors and pathogenesis of the mechanisms involved for the transition from health to this disease. This is especially valid in cancer, where the causative factors are not usually clear in the routine clinical cases, except, perhaps, in a few cases, where there is evidence for a genetic or a physical, chemical or biological involvement for cancer development. Cancer treatment follows a detailed and precise staging and grading of the established disease, but, often, with no satisfactory detection of the factors that transformed a previously healthy individual into a cancer patient.

The essential purpose of this book is to help in recognizing the causative factors in each case and in adapting treatment alongside these factors and the emerging model of cancer pathogenesis and regressability. The ever-increasing number of reported cases of a “spontaneous” regression of tumors do not reflect a biological curiosity or incidental events, but it is a strong indication that the defense mechanism against cancer can be effectively supported, when its nature is clarified and understood. The integrative cancer treatment would be optimized following the concept of cancer as a potentially reversible physiological stage and with the relevant principles and data of developmental biology, the thermodynamics of living

systems, systemic physiology, chronobiology and chronotherapy, always within the original framework of Hippocratic medicine.

CHAPTER ONE

THE PHYSIOLOGY OF THE HUMAN BODY

Homeostasis, Health and Disease

The term "homeostasis" was established through the work of Claude Bernard, the founder of modern physiology. Homeostasis is a process of dynamic balance regulated by organisms, through which they maintain an internal stability and adapt to the external environment for survival (Wang, S, 2022). The key concept, with which Claude Bernard is associated, is the *milieu intérieur*, the internal environment of the organism. According to Bernard, the stability of this internal environment is the condition for a free and independent life and it is the underlying principle of what would later be called homeostasis, a term also coined by Walter Cannon, by which he meant the product of the "coordinated physiological processes, which maintain most of the steady states in the organism."

Claude Bernard also posited that:

-The living body, though it has need of the surrounding environment, is nevertheless relatively independent of it. This independence, that the organism has of its external environment, derives from the fact that in the living being, the tissues are in fact withdrawn from direct external influences and are protected by a veritable internal environment, which is particularly constituted by the fluids circulating in the body.

-The constancy of the internal environment is the condition for a free and independent life.

-The constancy of the internal environment presupposes a perfection of the organism such that external variations are at every instant compensated and brought into balance. In consequence, far from being indifferent to the external world, the organism is, on the contrary, in a close and wise relation with it, so that its equilibrium results from a continuous and delicate compensation established as if it were the most sensitive of balances (Modell, 2015).

The living organism reacts unceasingly to the challenges of the environment, trying to remove any dangers and restore any injuries. So, whatever is called a "disease" in reality, represents the effort of the whole organism to stay healthy and the symptoms, as well as the functional and structural alterations, are nothing else, but reactions to noxious environmental stimuli. A "disease" should be defined as a necessary reactive process concerning the whole organism, even if the pathology seems focused and located in one or more specific organs or places of it, and is expressed with a highly individualized clinicopathological syndrome (CPS), which may include pathological entities recognized traditionally as "diseases", like chronic sinusitis, rheumatoid arthritis, ulcerative colitis, tumors, etc. (Wang, 2022). The reactive physiological processes of any CPS are, at first instance at least, beneficial phenomena for the whole economy, regardless of whether the patient feels unwell. Within certain sufficiently wide limits, any CPS supports homeostasis, so that its suppression is not at all the indicated therapeutic policy and may also be dangerous for the health of both the suffering organ and the whole organism. Certainly, when the reactive processes are intense, so that they may lead to undesirable effects and complications, a well-planned control of them is justified. In most cases, anyway, the treatment should guide the reactive phenomena with an integrative, systemic and individualized approach, always giving priority to any existing internal organ pathology (Qin, LZ, 2023; Vartholomaios, 2003).

The adaptation to environmental challenges and the maintenance of homeostasis constitute the fundamental condition and aspect of health. From the era of the famous physiologist Selye, stress is defined as a "general adaptation syndrome". Every structural and functional unit of the organism has adaptation mechanisms, which are coordinated, synchronized and integrated through processes, mainly of the nervous, immune and endocrine systems, that is of the information system of the whole organism (Lu, S, 2021). But, when stress is too prolonged and/or intense, the balance between the organism and the environment starts to shift against the organism. At this turning point, the health processes are expressed and perceptible by the patient as "symptoms" and by the physician as "signs". The normal phenomena do not change in quality, but only in quantity, in different grades in each case. However, when stressful conditions are prolonged, these normal processes lose their flexibility and their rhythms, their chronic order and their ability for immediate and quick responses to challenges and for a smooth return to the previous balanced condition (Elsenbruch, S, 2017). Providing that only quantitative and not any qualitative changes of the normal processes happen, the founder of pathology, Rudolph Virchow, as well as his successors, postulated that disease and health do not differ in the

quality and kind of processes, and that the "pathological" processes are in direct relevance and continuity with the physiological processes of health (Vartholomaios, 2003). The health and vitality of the organism are the end results of homeostatic regulation of the internal environment. The disruption of homeostatic mechanisms is what leads to disease, and effective therapy must be directed toward re-establishing these homeostatic conditions, working with rather than against nature (Billman, G, 2020).

The concept of homeostasis has experienced a dialectic period. The original theory of body equilibrium can be traced back to 460 BC, when Hippocrates first proposed the four humors theory to describe the balanced state of the human body. The science of the physiology of the human organism was established by Hippocrates, who argued that the material constitution of the human body, which supports its normal functioning, consists of four juices: blood, phlegm, yellow bile and black bile. This conception of Hippocrates became one of the fundamental medical principles that influenced medicine for centuries. It is characteristic that the four juices correspond to the four elements (fire, air, water, earth) which, according to the teaching of the pre-Socratic philosopher Empedocles, make up the physical environment (Kontopoulou, 2002; Vartholomaios, 2003).

Hippocrates realized the need to study the physiology of the human body through its structural elements. In particular, he argued that the material constitution of the human body consists of four juices (blood, phlegm, yellow bile, black bile), which are secreted by the four basic organs, namely the heart, brain, liver and spleen respectively. This conception of Hippocrates became one of the fundamental principles that influenced medicine for centuries (Chadwick, J, 1950; Billman, G, 2020). These "juices" correspond to surveying and integrative functional dynamics in the body, each one expressing a distinguished quality and a distinct kind of action. The role of juices in the human body is decisive, as their harmonious mixing contributes to maintaining health. If one of them is either in excess or in short supply, then a deviation of the body's condition towards a pathological state occurs. Therefore, the elements that make up man are not mixed at random, but in the right proportion, so that the composition of the body promotes health (Kontopoulou, 2002). The recognition that the correct proportion of juices in the body is the prerequisite of health leads, with the introduction of the science of physics and mathematics, into medicine, a fact that is certainly recognized today. The principle of balance between these "juices", these basic material constituents and functional qualities of the organism, for the maintenance of health, is highly reminiscent of the main homeostatic processes in the organism, controlled by endocrine, neurophysiological and

immunological processes, as they are described in modern physiology (Vartholomaios, 2003).

According to Carrell, a "disease" consists of a functional and structural disorder and its aspects are as numerous as our organic activities. There are diseases of the stomach, of the heart, of the nervous system, etc., but in illness the body preserves the same unity as in health. The body is sick as a whole and no disturbance remains strictly confined to a single organ. Since physicians have been led to consider each disease as a specialty by the old anatomical conception of the human being, only those who know people both in parts and in totality, assessing simultaneously all the anatomical, physiological, and mental aspects, are capable of understanding when an individual is sick (Carrell, A, 1935).

The quintessence of homeostasis is the functional and structural integrity of the totality, of the whole organism and the individuality, as these principles are thoroughly described and supported in Hippocratic writings (Vartholomaios, 2003). Perfectly aligned to these Hippocratic holistic principles, the founder of modern physiology, Claude Bernard declared:

> Physiologist and physicians must never forget that a living being is an organism with its own individuality. Since physicists and chemists cannot take their stand outside the universe, they study bodies and phenomena in themselves and separately, without necessarily having to connect them with nature as whole. But physiologists, finding themselves, on the contrary, outside the animal organism which they see as a whole, must take account of the harmony of the whole, even while trying to get inside, so as to understand the mechanism of its every part. The result is that physicists and chemists can reject all idea of the final causes for the facts that they observe; while physiologists are inclined to acknowledge a harmonious and pre-established unity in an organized body, all of whose partial actions are interdependent and mutually generative. We really must learn, then, that if we break up a living organism by isolating its different parts, it is only for the sake of ease in experimental analysis, and by no means in order to conceive them separately. Indeed, when we wish to ascribe to a physiological quality its value and true significance, we must always refer to this whole, and draw conclusions only to its effects in the whole. (Bernard, 1865; Billman, 2020)

The principles of homeostasis applied in respect to the totality and individuality should be the basis of any therapeutic intervention in all diseases generally and in cancer specifically. Any cancer treatment, surgery, chemotherapy, radiotherapy, etc., should, as much as possible, be aligned to

and follow these principles, considering the pros and cons of its application in each individual case.

Form, Space, Place and Time in Physiology

Initially in embryogenesis, the fertilized ovum or zygote is not a simple cell, it is the entire organism, which first cares to establish a three-dimensional form with the appropriate orientation within the three-dimensional space, so that there is a priority of spatial planning over the development of form. It has been postulated, as a basic biological and physiological principle, that "form is the function of the locus" (Nicholson, 1950), which means that the "locus" in the space primarily defines the kind of "function" and that the "form" is the final outcome of the arrangement of the functional processes in space and time, as initially happens in embryogenesis (Shahbazi, M, 2020). In every formation, healthy and benign or diseased and malignant, that develops in the body, there is always a precedent functional process with the appropriate and necessary spatial and time arrangement for the development of the form that develops afterwards. All formations, including normal organs and tissues, as well as tumors, are faithful and exact images of the precedent functional processes in space and time. For instance, an intestinal adenomatous polyp has a cauliflower appearance according to the arrangement of the precedent functional process for growth in space and time; it is just like a tissue architect has drawn up a plan and then the tissue engineer has exactly constructed whatever the architect has planned. Structure and function are a biological entity; structure may be seen as crystallized function and function as structure in motion.

According to Carrell, the associations of cells, as revealed by scientific techniques, are of enormous structural complexity and tissues are of great structural heterogeneity, but they behave like a perfectly integrated being. The complexity is artificial, since it is created by the techniques of observation. Each organ is not limited by its surface. It possesses multiple activities and takes part in almost all the events of the body. The spatial and temporal dimensions of each gland are, in fact, equal to those of the entire organism. In short, the body is an anatomical heterogeneity and a physiological homogeneity (Carell, A, 1935).

A holistic picture emerges of interactions and forces that maintain the integrity of tissues, organs and the whole organism. The "sympathy" of all parts of the body, as conceived by Hippocrates, responds absolutely to a systemically integrated totality. At the tissue material level, the generation and maintenance of form is the outcome of the interaction between cells and

their extracellular matrix, at the organ level between the tissues of the organ and, finally, between organs at the whole organism level. Accordingly, the structure of the cells of a part of an organ is a "function of position". This means that cells do not undergo differentiation in a given direction because they must obey a preordained destiny. They do so in response to an orderly sequence of certain specific factors, constituting the normal environment. When this sequence is of the right kind, development proceeds in the appropriate and normal direction. If this orderly sequence is disturbed or interrupted, development proceeds in a new direction, which, although "abnormal", is the only one appropriate for the new or abnormal environment, which, when acting long after embryonic development, may give rise to the so-called heterotopic tissues (Nicholson, 1950). This process, called "metaplasia", is the most common in the category of anomalies of position, characterized by normal tissues found in unusual sites. Metaplasia is the outcome of the dedifferentiation of local cells at a site, a process of returning to a primary undifferentiated state, which is followed by re-differentiation to a different cell type, which is normally accommodated at another site of the organism.

Metaplasia is of special importance, since it expresses the need for specific changes of function and structure at a site and the subsequent development of cells of a remote site, that serve the above need. Like every physiological reaction that takes place, metaplasia is objectively and necessarily physiological, since it is the only possible reaction for the given environment. The cells undergo metaplasia for the sole purpose of keeping the local and general economy more compatible with normal living phenomena (Teal, E, 2020). Typically, metaplasia is triggered by environmental stimuli, which may act in concert with the deleterious effects of microorganisms and inflammation. Metaplasia arises in originally normal tissues in a number of pathological states, most of which are associated with irritation and inflammation of a more or less chronic kind. A hallmark of metaplasia is a change in cellular identity. It has been demonstrated that metaplasia is often a precursor to low-grade dysplasia, which can culminate in high-grade dysplasia and, possibly, cancer (Giroux, 2017).

Metaplasia might be rightly called a "metamorphosis" and responds to the needs of a "heterotopic regeneration", since the new cells are normally habitats of another site, but they are produced, as most suitable, in response to an abnormal environment. The normal degree and direction of differentiation of the cells of the body depend upon their site and environment. If the environment becomes pathological, the cells, even of the fully developed adult body, react to it by alterations of the extent or

direction of their differentiation and of their specific properties, as this exactly happens in metaplasia (Goldenring, JR, 2022; Nicholson, 1950).

The time factor has a profound impact, through the maintenance and appropriate adaptation of normal rhythms, on the needs of the body and on the proper timing and synchronization of functions, processes and spatial relationships between parts of the "inside" and/or between the "inside" and the "outside" of the organism. Chronophysiology is a segment of chronobiology, that studies the time dimension of the organization of physiological processes of the organism and explains how the biological systems and processes of organisms relate to each other with regard to time. The time factor is basically displayed in two aspects:

-Physiological rhythms and their synchronization.
-Processes of synchronicity or equivalence.

Physiological rhythms dictate the regular appearance of similar quantities and qualities at similar time intervals, so that their quintessence is the close cross-talk between space and time, where all physiological phenomena occur. They constitute the basic expression of the time factor, that allows the proper communication, through various signalings, between cells, tissues, locations and organs. When their functioning is suppressed and/or becomes irregular, then the functional and structural identity of living tissues is threatened and this is also expressed in deteriorations in differentiation and growth dynamics and equilibria, conditions especially related to tumor development.

The inner circadian clock enables the human body to anticipate events that are repeated daily and to adapt to any new and different environmental circumstances in a physiologically optimal manner. Almost all vital processes of the body are subject to various rhythms. The critical role played by circadian rhythms in maintaining both systemic and tissue-level homeostasis is well established, and disruption of the rhythm has direct consequence for human health, disorders and diseases (Ayyar, 2021). Even the stages of acute illnesses and the intensity of their symptoms follow the impulses of an inner clock. A disrupted circadian clock has been linked to an increasing susceptibility to several pathogen-associated diseases, and the interplay between viral infections and the circadian clock is of increasing interest with an expansion of work in this area. The rhythmicity of immunometabolism has become a key aspect of immune defense and disease outcomes. On the other hand, as the host circadian rhythm can influence virus replication, virus infection can perturb the host circadian

system (Borrmann, 2021). Given the interplay between a virus and the host circadian mechanism, host susceptibility to infection or disease is not only dependent on the infectivity of the viral inoculum, transmission route and length of exposure, but also on the time of day when the pathogen is encountered. Specifically, it seems that the interplay and cross-talk between circadian rhythms and viruses may be specifically important in the evaluation of the involvement of oncogenic viruses in the process of carcinogenesis (Zhuang et al., 2017).

Any serious disturbance of the circadian rhythms must always be assessed and evaluated, since general health and wellbeing are strongly impacted by it. Under these circumstances, tissues are not sufficiently supported to adapt their biological function and to anticipate external changes through the synchronization of their physiology to the environment. It has been demonstrated that the disruption of circadian rhythms may increase to critical levels the susceptibility of tissues and organs to various external stimuli, that may act as occasional, but determining factors in the pathogenetic chain of a disease generally and cancer specifically (Fishbein, 2021).

The circadian system relies on the presence of a molecular clock in every organ and every cell of the body, thus generating multiple autonomous clocks. All these self-sustaining clocks are synchronized by a central molecular clock within the suprachiasmatic nucleus (SCN), composing a hierarchically structured circadian system (Gillette, 1999). SCN neurons have distinct, topographically organized mechanisms, which allow them to remain synchronized to one another and they generate a pronounced circadian rhythm of neuronal firing frequency, which allows them, through a variety of direct and indirect output pathways, to synchronize other cells throughout the body. Thus, the SCN master pacemaker synchronizes to the light/dark cycle, and in turn synchronizes other subsidiary cellular oscillators (Welsh, 2010). The SCN, this master synchronizer is located in the anteroventral hypothalamus, where it receives external light information derived from the retina as well as non-light information from the other tissues and organs of the body. The SCN integrates all this information and generates output signals to the peripheral clocks, setting the basis for a most precise and important coordination between the tissues, beyond the harmonization of all to the 24-hour day (Astiz, 2019). Although peripheral clocks act with a certain autonomy, their orchestration via the SCN is necessary to coordinate a network between peripheral clocks. The SCN coordinates peripheral clocks directly through humoral and synaptic signals (Crespo et al., 2021).

According to Jung and Pauli, natural phenomena are ruled not only by the principle of causality, but also by a kind of natural order that interconnects and regulates all events, which was designated as the “principle of synchronicity or equivalence”, or in brief, SE. "Synchronicity" is an etymologically restricted term which implies that two apparently related but causally unconnected events have occurred at the same time. Synchronicity, working through various physiological rhythms, is a dimension that is additional and complementary to causality, which adds new qualities, coherence, proper timing and meaning to otherwise diffuse and heterogeneous phenomena, like so many that are described very thoroughly in detail in modern literature, mainly in the fields of biology and biochemistry (Atmanspacher, H, 2020). The application of the principle of SE on living systems has been called “chronobiology”, in medicine “chronomedicine”, in physiology “chronophysiology” and in pathology “chronopathology”. It has been proposed that the perception of SE would be possible thanks to the presence of certain reflexes located in areas of the central nervous system, responsible for aligning the body to world rhythms (Musso, 2017). According to Schopenhauer, the development of world events is coordinated by causality and synchronicity in a way similar to the intersection of parallels and meridians at geographical locations (Combray, 2009). From this perspective, phenomena are subjected to a causal order (linearity), which would be deployed under the influence of a cyclic pattern affecting the time and space in question (Musso et al., 2007; Combray, 2009).

SE is related to the Hippocratic principle of “sympathy”, by uniting diverse spatial and time factors and qualities between adjacent or remote loci of the organism within a single and unique functional framework. “Sympathy” according to Hippocratic treatises is a surveying and meaningful dynamic, interconnecting anatomically remote and unrelated structures of the body. An example of this Hippocratic “sympathy” is that described in a Hippocratic treatise between the cervix uteri and the breast, where suppressions of physiological reactions of the first may lead to serious pathologies of the second (Vartholomaios, 2003; Kouzis, 2004).

The space dimension of the organism is mainly represented by the extracellular space or stroma, which is occupied by a flowing substance, the extracellular matrix (ECM) (Kular, 2014). Structurally, the ECM is divided into two main parts, the basement membrane and the interstitial matrix. The basement membrane is produced and organized by epithelial, endothelial, and stromal cells and supports their structural and functional integrity. The interstitial matrix is mainly produced by stromal cells and is highly charged

and hydrated due to the major presence of fibrillar collagens, proteoglycans and glycoproteins, like hyaluronan (Hoye and Erler, 2016). The ECM provides biophysical and biochemical cues regulating cellular proliferation, differentiation, migration, etc., and creates a dynamic environment that constantly influences cellular responses.

The main constituent of the ECM is heparan sulfate (HS), a linear polysaccharide with various sulfation modifications. HS is covalently attached to core proteins to form HS-proteoglycans (Fuster, MM, 2010). Heparan sulfate is one of the most informationally rich biopolymers in nature. It may have an enormously diverse structure, which exhibits a considerable number of unique overlapping sequences with peculiar sulfation profiles. The heparan sulfate sequences are not directly encoded by genes, but are created by elaborate biosynthetic mechanisms, which ensure the generation of these indispensable sequences (Sugahara, 2002).

HS-proteoglycans (HSPGs) are important cell surface and ECM substances involved in the orchestration of multiple cellular events in physiology and pathology. The structural features of HS chains, including length and sulfation patterns, are crucial for the biological roles displayed by HSPGs, as these features determine HS chain binding affinities and selectivity. The HS structural diversity results from a tightly controlled biosynthetic pathway that is differently regulated in different organs, stages of development and pathologies, especially cancer (Marques et al., 2021). HSPGs play a fundamental role in most biological functions by interacting with proteins of whatever kind and according to the needs of the economy, regulating and integrating the flow of information through signaling.

HSPGs are present at the cell surface as glycocalyx, within the pericellular environment and in the extracellular matrix. These very different locations combined with their structural diversity enable them to participate in a large variety of cell and tissue processes (Jin, 2021). Though the basic biosynthesis of HS takes place within the Golgi apparatus of most cells, the post synthesis of innumerable variants of HS takes place in the extracellular matrix through the action of specific enzymes. This is a most interesting process, since it evolves in the absence of genetically encoded information and is a non-template-driven process, unlike other biopolymers (DNA, RNA, polypeptides). This means that the extent of modification reactions that the glycan chains may undergo, and the consequent HS final structural motifs, are not directly encoded in the genome. The structural features resulting from each stage of HS biosynthesis determine the subsequent “step-by-step” finetuning of the HS overall structure (Annaval, 2020).

Many aspects of the HS biosynthetic scheme are shared by the structural analog heparin, which is synthesized exclusively in the granules of mast cells and has a several-fold higher degree of polymerization and more extensive modification than HS (Kitagawa, 2002). The granule constituents of mast cells are packaged efficiently with the help of heparin, the highly negatively charged HS derivative (Herrera-Heredia, SA, 2022). Heparinase (Hpse), secreted by degranulating mast cells, has been identified as the sole HS degradation enzyme that generates fragmented oligosaccharide HS. These fragmented molecules can be taken up by mast cells, like other extracellular materials, to synthesize heparin. Hpse is also essential for heparin processing in mast cells. The Hpse-mediated cleavage liberates the heparin chain from a core protein and generates fragmented heparin (Shi, J, 2024).

With a proper fit of the above mechanisms, a functional system emerges which performs the highly sophisticated and important storage and recycling of acid mucopolysaccharides, maintaining a balance between HS in the extracellular matrix and heparin in the mast cells. In conclusion, the degradation products of HS, the quintessence of the extracellular matrix, are stored as heparin in the granules of mast cells, which when needed, may be excreted by the mast cells and transformed into the required kinds of acid mucopolysaccharides, especially of HS. These mechanisms are especially important in the maintenance of the structural balance of tissues and in certain chronic diseases and disorders, especially cancer.

Systemic and Energetic Physiology

The organism is a system; its problems are not static but dynamic and cannot be solved by morphological methods alone. The living organism is a system in unstable equilibrium. A state in equilibrium is, in fact, dead (Trevors, 2011). Organs and organ systems cannot be seen as simple complexes of cells alone, which are the last functional unit, following faithfully the functional and structural needs and demands of the tissue and organ, where they reside (Hanselmann, 2016). Although individual cellular and molecular functions are certainly important in their specific roles, a much higher understanding of life phenomena can be achieved by employing a “systemic physiology”, that sees the organism as a living system. “Sympathy” between the parts of the body, as conceived by Hippocrates, responds absolutely to the properties of a system, of an integrated totality.

A system is an integrated whole consisting of parts, whose properties are much more limited than those of the whole. The organism is an integrated

totality with the properties of a system. But also, each organic system is a "system", each organ is a "system", each tissue is a "system" and each cell is a "system" on its own. Hippocrates recognized that each anatomically distinct part of the body would be a system on its own according to the selected level of study of the organism and that the properties of a system are lost when the system is physically divided into individual and isolated constituents. Each one of these "systems" has the properties of the whole, of the totality, when it is or should be the object of a research or clinical intervention, so that wholeness or totality is a matter of the selected and/or indicated focusing level of the observer (Vartholomaios, 2003). This level is many times an organ, especially one of those organs that reveal a tendency for "autonomy or hegemony" in the organism. The value of a person's life may be equal to that of his weakest vital organ: here, the particular organ is equal in importance to that of the entire organism (Burnett, 1992).

Three basic dynamic participants that play the central role for the maintenance of homeostatic balance are energy, information and matter. Each of these three factors is equally important to the cell and they are all reciprocally dependent. Energy loss, disturbance of information or changes in the composition of matter may irreversibly deteriorate cellular functions, leading to increased local entropy and disorder, energy dissipation and information reduction. In terms of physics, these changes may lead to a state where the system gets irreversibly imbalanced, but is thermodynamically more stable. When a return to the original order state is not possible for thermodynamic reasons, the cells either die or they enter a process that leads to a progression of disordered cells with different characteristics, possibly with autonomous and aggressive behavior, like that of cancer cells (Hanselmann and Welter, 2016).

In a closed system, entropy either stays the same or increases. Within any isolated system, which is either closed (i.e., there is no interaction of energy or matter with its environment) or includes the system and its environment, if there is interaction, the change in entropy is universally positive (i.e., greater than or equal to zero) according to the second law of thermodynamics. The cell is an open thermodynamic system, it can exchange both matter and energy with an outside system (the extracellular environment) and release degradation products (positive entropy) such as CO_2, H_2O, heat and other thermodynamic waste. Because of that capability, the cell can maintain and increase cellular order within a progressively entropic environment (Lifson, 1997).

During embryogenesis, there is the onset and development of complexity and self-organization of the new living entity, which is still a closed system, characterized by exponential growth, the presence of significant angiogenesis and temporary protection from immunosurveillance of the large open system with which it is connected, i.e., the mother, and it exists during the time-limited gestation; when sufficient complexity and self-organization are present, the closed system must become an open system, which takes place during birth (Hanselmann and Welter, 2016).

In living systems, two types of mechanism causing entropy change may be described: a) irreversible processes described by the second theorem of thermodynamics always causing positive or zero changes in entropy, i.e., an increase in the disorder of the system, and b) controlled regulatory processes of a living system conditioned by metabolism and communication with the surrounding environment. The overall change in the cellular entropy caused by these regulatory mechanisms is always negative, as the living system maintains or increases the orderliness of its structure through them (Viswanadham, 1968). Living systems are characterized by the ability to maintain or even reduce their degree of disorder and ensure the stability of their internal environment in terms of structure, chemistry and energy. Living non-equilibrium systems that are complex must continuously produce entropy over time to create a healthy internal emergent order. In striking contrast to non-living systems, nature and life are characterized by the continuous creation of remarkably ordered complex systems that are far from thermodynamic equilibrium. In fact, it is precisely by continuously producing entropy (i.e., degrading energy gradients) that life spontaneously creates its internal order.

Metabolism, which is the "burning" of oxygen along with organic compounds such as glucose to carbon dioxide and water, is the principal means to produce heat and entropy (Seely, 2020). Metabolism corresponds to a set of life-sustaining reactions that are doomed to generate entropy. The conversion of food into energy and heat (catabolism) generates a large entropy flux. Heat is then released in the environment. Entropy is also transduced into the building blocks of life such as proteins, membranes or nucleic acids (anabolism) with the elimination of waste. If one considers the cell as the inside, to comply with the second law of thermodynamics, the excess entropy must be exported outside the original cell (Sabater, B, 2022). The excess entropy can be exported either in the form of radiation (heat) or in the form of matter called biomass in biology. Biomass can be exported in the form of the extracellular secretion of molecules. Entropy of the primary cell can also be released in the form of a daughter cell. The division of the

primary cell into two different entities decreases by two the entropy of the original cell. Thus, entropy can be released either in the form of heat or in the form of supplementary cells and/or cellular waste. Heat will be released outside the body, but waste and biomass will stay outside the original cell but inside the body (Schwartz, 2020).

A prerequisite for the existence of living systems is the constant exchange of energy and matter with the surrounding environment. Therefore, living systems are open systems from the thermodynamic point of view, so they do not contradict the second law of thermodynamics, which allows a zero or negative change in entropy for open systems (Trevors, J, 2011). A living system reaches true thermodynamic equilibrium only after its death, when the regulatory functions cease and the entropy of the now non-living system increases until it reaches a maximum due to the action of irreversible processes (Briedis, 1984).

The stability of the environment at the cellular level is ensured by the constant activity of cellular metabolism, conditioned by obtaining energy from sunlight directly or indirectly. This energy is used to synthesize more complex substances from simpler, energy-poor precursors, which reduces the entropy of the system. In parallel, the opposite process takes place, that is the breakdown of energy-rich complex substances and their subsequent processing with the simultaneous release of energy. Part of this energy is again used by anabolic processes, but part is released into the environment in the form of heat or other forms of energy (Kaufmann, 2009). The positive change in entropy is thus distributed between the cell itself and its surroundings. The cell thus increases its degree of order, that is its total entropy change is negative. However, the absolute value of this change, in accordance with the second theorem of thermodynamics, does not exceed the positive change in entropy of the isolated system of the cell and its surroundings (Ricard, 2003).

Entropy should not be considered a “measure of disorder”; a more accurate and helpful way of envisioning entropy is through its proclivity to eliminate energy gradients. Entropy of a living system would be seen as the liveliness of the system, which, anyway, has to be expressed in the environment at a pace analogous to its production rate. So long as the living system maintains its order and homeostasis, the entropy of the system is synonymous with “life”. If the accumulation of entropy increases disproportionately to its release to the environment, due mainly to suppression, and the liveliness exceeds certain predestined limits, the entropy changes its face and kind and turns in a deadly disorder, which may reach levels incompatible with life

and finally lead to death (Ulanowicz, 2019). The living cell, being a material system, should comply by releasing entropy either into the body or into the outside environment. In the case of pathologies, entropy cannot be fully exported outside the body and stays inside the body either in the form of intracellular biomass, or extracellular waste products (Schwartz et al., 2020). A new way of classifying diseases has been proposed, looking at the kind of entropy which cannot be easily excreted outside the body. In such a classification, inflammatory diseases play with entropy through increased heat, biomass synthesis (the proliferation of lymphocytes and neutrophils) and the secretion of pro-inflammatory proteins, waste products from the cell's point of view. Specifically, during acute inflammation there is increased heat, synthesis of biomass and increased waste secretion (Schwartz et al., 2020).

According to D'Arcy Thompson, when one seeks in a structure only the beginning and the end of the human body, one is apt to fall into the error of attributing to matter what is due to energy and is manifested in force; or, more strictly speaking, of attributing to material particles individually what is due to the energy of their collocation. The "energy of their collocation" corresponds to the complexity and auto-organization of the human body as a system, functioning through appropriate information processes and preventing the increase of entropy (Thompson, 1952).

It is important to be noted that the functional relationship between organs can be investigated through the information systems. The conventional information systems are based on anatomical, biochemical, neurological and immunological connections and have an unquestionable importance in any patient case history for the investigation of the pathogenesis of any disorder or disease. The information systems allow the so-called pathogenetic chains to be followed and may be based on both the conventional anatomical pathways and physiological processes, like the neurophysiological connections at a neurotome/myotome and, also, to the unconventional channels of certain integrative and holistic disciplines, which have, anyway, already offered the necessary clinical evidence of validity. Classical examples of unconventional information systems are the "meridians" of Chinese medicine and the "veins" of Hippocratic medicine, which often have common pathways. The investigation of any case history incorporating the above systems and channels proves to be especially effective when a "suppression" of a physiological process in an organ or part of the body leads to a serious pathology in another, often remote and anatomically unrelated, organ or part of the body. The subject of "suppression of symptoms" is extensively described in Hippocratic medicine and Chinese

medicine, with almost the same meaning and assessment (Vartholomaios, 2003).

Individuality is a very essential aspect within the framework of systemic and energetic physiology. In the modern history of medicine, the concept of "personalism in medicine" was supported from the first decades of the 20th century, while the discipline of "individual physiology" was introduced some decades later (Schaefer, 1979). The understanding and assimilation of the concept of individuality in physiology are very important for the understanding of the changes in health and disease of each individual and are based on existing trends in physiological functions with their individual peculiarities, like those related to predispositions and susceptibility to disorders and diseases. It seems essential to complement conventional applications with an integrative, systemic and holistic approach for obtaining a more objective image of health and disease, wider than that recognized by the cell theory alone. Certainly, Hippocratic medicine may be used as the ideal model for an upgraded, as above, and individualized approach of patients in diagnosis, treatment and prognosis (Vartholomaios, 2003).

Systemic physiology is under the surveillance of two organ systems of major importance, the nervous and the haemopoietic systems. There is an interesting interplay of the nervous system with bone and bone marrow. Bones provide skeletal scaffolding and space for both the central nervous system and the hematopoietic system. The bone marrow microenvironment contains specialized niches responsible for the maintenance of hematopoietic stem cells (HSCs), which generate all blood cell lineages throughout life. At a steady state, most HSCs are maintained in a quiescent state within their niche. In response to stress, such as radiation injury, chemotherapy, infection, etc., HSCs become activated to restore homeostasis (Maryanovich, 2018). Besides, bone marrow derived stem cells are distributed at almost every organ and there is increasing evidence that they have a very active and decisive role in local tissue economy. The importance of neural signaling in hematopoietic homeostasis, inflammation, and cancer has been thoroughly reviewed. It has been demonstrated that the nervous system regulates bone remodeling and metabolism as well as hematopoietic homeostasis. In the hematopoietic system, the autonomic nervous system regulates stem cell niche homeostasis and regeneration (Hanoun et al., 2015).

Many studies have confirmed both autonomic and sensory nerve innervation of the skeleton that reach deep into the bone marrow space. Autonomic

nerves reaching the bones penetrate the bone marrow, reaching deep into regions of hematopoietic activity. Out of all the autonomic nerves that reach the bone, it was shown that only close to 5% of sympathetic nervous system (SNS) nerves actually penetrate the bone marrow. However, considering the relative volume of the bone cavity compared with the periosteal bone region, the bone marrow contains the highest density of autonomic nerves (Elefteriou, 2018). Initial evidence that SNS nerves regulate hematopoiesis emerged from studies describing a positive correlation between bone marrow circadian oscillations and the proliferation of hematopoietic cells. The SNS represents a decisive regulatory component of the bone marrow microenvironment, where sympathetic nerve fibers and other neural crest derivatives form a niche, essential for maintaining hematopoietic stem cell (HSC) behavior in stressful situations (Maryanovich et al., 2018).

Beyond the production of blood cells, bone marrow seems to have an even more systemic role and importance in the organism, as this is witnessed by the presence of HSCs in many extramedullary sites of the organism. This presence has been explained as taking part in the migration of hematopoietic stem cells through the blood, to different organs and to their bone marrow niches. The active navigation of HSCs is a process termed "homing". Similarly, homing is required for seeding of the fetal bone marrow by hematopoietic progenitors during development. Homing has physiological roles in adult bone marrow homeostasis, which are amplified during the stress-induced recruitment of leukocytes from the bone marrow reservoir and during stem cell mobilization, as part of host defense and repair (Lapidot et al., 2005). In extramedullary sites, the role of local HSCs for the structural economy of all tissues and organs of the human body seems to be essential and decisive. The local population of normally habitant HSCs in extramedullary sites should be especially considered in any emerging structural deviation of tissues, as it happens impressively in the case of cancer.

Systemic and energetic physiology has been over the last decades enriched with an upgraded conception concerning the so-called "morphogenetic field", an obviously involved biophysical template and plan behind any structural rearrangement in all the development and differentiation processes of the tissues of the body. Morphogenetic fields seem to be fundamental in the tissue and organ economy and, though they were considered in the past with skepticism as something metaphysical, it became necessary in the last decades to adopt them as a framework for the understanding of any transactions in tissue architecture, especially in certain serious pathologies like cancer.