Professor Dr. h.c. **Rudolf Klimek** is a disciple of Professor Bolesław Skarzynski whose assistant he was for 6 years (1952–1957). Professor Skarzynski as an assistant professor at the University in Stockholm wrote together with the Nobel Prize laureate, Hans von Euler a book "*Biochemistry of Neoplasms*" (Biochemie der Tumoren, F. Enke Verlag, Stuttgart, 1942). With this work the era of the molecular biology in the whole medicine was initiated.

R. Klimek described in 1963 post-partum hypothalamic insufficiency syndrome, characterized among others by more often (10–20%) precancerous states and cancers of the cervix uteri. R. Klimek was first in the world to apply natural hypothalamic hormones in the therapy of this syndrome confirming their effectiveness by the clinical observation with the double blind-control group. (Klimek R.: Les resultats therapeutiques des cas du syndrome hypothalamique postgravidique. Actualites Endocrinologiques. 1968, **9**, 195) In 1976 R. Klimek was promotor of a doctor honoris causa degree of Andrew Schally who, among other things, in the next year was rewarded with the Nobel Prize for the description of the structure and synthesis of these hormones.

In the same year, 1977, I. Prigogine received the Nobel Prize in Chemistry for the discovery of the self-organizing dissipative structures. This discovery was used by R. Klimek to explain the mystery of origin of cancer and caused by it the neoplastic diseases.

From the point of the view of the medical thermodynamics this new theory unifies all so far existing theories of cancerogenesis and clearly distinguishes a cause of the cancer as the state of the organism's cell in the bifurcation point of the cellular dissipathogenic states, in which a cancer is an alternative to death. At the same time his thermodynamic theory explains mechanisms leading to the disease, and as based on the thermodynamics, it was confirmed by studies on MRI conducted together with P. Lauterbur, a creator of the nucleomagnetic imaging.

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INVITED NEL REVIEW

Biology of Cancer: Thermodynamic Answers to Some Questions

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Abstract All the theories of carcinogenesis have properly described this event from methodologically different points of view (medical, biological, social, biochemical psychological etc.). The point is that one should understand the thermodynamical rules underlying each of these approaches. On this level of knowledge, quantum thermodynamics combines matter and energy, while technical quantization in a novel way differentiates precancerous states as the dissipathogenic ones from the neoplasms as the newly formed dissipative structures (systems). From the essential nature of the neoplasm one can derive some general rules of therapy which focus mainly on: 1° prevention and therapy of the dissipathogenic states, 2° strengthening of the regenerative and defensive mechanisms of the organism and, finally, 3° removal of neoplastic changes as widely as necessary but also as sparingly as possible. For a long time, these rules have been observed in reverse order. That cannot improve the medical outcome, which has not changed for a few dozen years, i.e. recovery depending on the clinical level at the moment of the diagnosis.

Introduction

In 1858 R. Virchow introduced the cellular theory into medical sciences and formulated the famous aphorism "Omnis cellula e cellulae". Hence, the human pathology reached a cellular level, but it seems necessary top emphasize that for too long the cell has been regarded as a basic body structure analogously as an atom is regarded as the basic component of chemical compounds. However only rarely does one bear in mind that atoms as integral parts of chemical compounds represent also and possibly to a greater extent a part of living organisms. Currently, due to the use of Magnetic Resonance Spectroscopy and Imaging (MRIS) atoms can be the object of safe direct investigations in various states of health and disease.

The smallest known microsystem consists of atoms which build a structure showing just living system patterns and underwent not only physical and chemical but also biological laws. This approach suggests that a cell can no longer be regarded as the smallest microsystem of the human body.

The human organism, just as every macroscopic system is composed of microsystems. From the thermodynamic standpoint every microsystem in relation to other systems may remain in three separate physiological states, that is, the equilibrium, the near-equilibrium and the far-from-equilibrium state. All structures being in the equilibrium state remain stable and resistant to small perturbations. The near-equilibrium state undergoes evolution until it reaches the new stable state but its spontaneous evolving into a new structure is not possible. On the contrary the system being in the far-from-equilibrium state undergoes disintegration or may and sometimes even should self-organize into a new dissipative structure, taking from the environment and dissipating significant amounts of both energy and matter. This structure is characterized by a capability to a spontaneous transformation into more and more complex ones what represents a natural phenomenon occurring not solely in living organisms [1].

At the beginning of the century the theory of relativity and quantum mechanics were introduced but it was only the discovery of MRI which made possible to prove the existence of quantum thermodynamics, which I used in my thermodynamic theory of cancer [2-7]. My own earlier research on neurohormonal conditioning of the cervical cancer, which I had conducted for several years, paved the way for an entirely new general thermodynamical interpretation of neoplasm, characterized in each case by a unique biological environment [8-11].

As for the lack of understanding of the essence of the cancer as a self-organizing dissipative structure according to quantum thermodynamics, it is the patients who pay the price with their health and life. Therefore after over twenty years of attempting to convince the society of the naturalness and thermodynamically inevitability of carcinogenesis I decided to answer to some oncological questions once again.

Cancer as a self-organizing biological system

Each biological system e.g. a cell in the human organism in order to exist has to exchange matter and energy through its walls with the environment, which is accompanied by the production of entropy. In the case of restriction of the access of oxygen or other substrates necessary for the metabolism of the cell, it will reduce or terminate additional functions, thus minimizing the production of entropy. However, further minimization of the metabolism of the cell on the branch of the possible far-from-equilibrium internal states leads to the so-called bifurcation point, beyond which the given system cannot continue to exist in the current environment. According to the physical laws, only a system which is better organized (i.e. produces less entropy while increasing the dissipation of matter and energy in the environment) can exist. Neoplasm is such a new self-organizing dissipative structure in the multicellular organism, formed in the place and out of the parts of the past system, which on the branch of its internal thermodynamic states found itself at the bifurcation point. It is known that the environment has an active role in this process, since each self-organized system has to produce less entropy at the expense of its increase in the environment.

Unicellular organisms, when confronted with an environment entirely different from their biological nature, at the bifurcation point of their thermodynamical branch either die or self-organize themselves into new types of cells capable of continuing their existence in an environment which makes life of so far existing cells impossible. The mutation is a good example of their alternative to death. The situation is different when we view the originating cancerous process on the level of a cell in a multicellular organism. Every single cell which appears due to many different causes at the bifurcation point before its sudden or programmed death can prolong its biological existence only as a new dissipative system with its unique identity. It must, however, be adjusted to its entirely unique biological (i.e. living) environment, which does not occur with respect to unicellular organisms. Owing to the unique identity of the entire organism, according to the laws of nature in a stochastic way there appears neoplasm as a new biological system also with a singular, unique identity. It means that it can exist and develop only within this

particular organism, at the same time increasing dissipation of mass and energy therein, which leads to the death of this organism and thus to the end of the neoplasm's own existence, too. This limitation does not concern unicellular organisms.

Diagnostics of cancer states

Neoplasm is an alternative to cellular death in the multicellular organism but - as a newly formed dissipative system – it has its own equally unrepeatable thermodynamical branch which as stochastically matched is not a simple continuation of the previous one. The most characteristic feature of such a system is its distinct isolation from its closest environment, even a pathologically changed one. Furthermore, it is possible to indicate in the tissues different and sometimes simultaneously appearing types of neoplastic cells. The rich morphological literature describes many indirect more or less pre-cancerous states, but distinctly presents cancer as something different.

Thermodynamic theory of carcinogenesis not only differentiates clearly its cause from its pathomechanism but, most importantly, eliminates the necessity of using artificial division of the same atoms, molecules or ions just because they found themselves in the body cavities, circulating blood or in cellular secretions. It would suffice to place an organism in a permanent magnetic field and induce magnetic nuclear resonance to observe and examine the organism literally on the atomic level. We measure the reactivity of identical atoms independent of their spatial localization but taking into account their conditioning by such different factors as e.g. velocity and composition of blood, rate of gas perfusion or level of enzymatic activity as biocatalizators in the organism as a whole. The last of the above responsively determines the state of each atom or ion in the organism. Together with the inventor of MRI P. Lauterbur already in 1981 we confirmed the dependence of the time of NMR relaxation from precancerous and cancerous states [12-14] what confirmed thermodynamical interpretation of both the cause and complex mulitifactorial conditioning of the neoplastic disease.

Unfortunately, physicians still continue to treat their patients relying on physical categories from the nineteenth century and prefer cause-and-effect reasoning to the holistic (and thereby probabilistic) conditioning of events. They prefer to see cancer in CT/PET rather than to change their way of thinking, which would enable them to see the sites of its most probable origin, metastasis or recurrence by means of MRIS (Magnetic Resonance Imaging-Spectroscopy).

New therapeutic rules

The state of the immediate environment determines the formation and further development of neoplasms. The state of equilibrium or close to equilibrium provide conditions for effective self-defense of organism in contrast to the states far to equilibrium i.e. the dissipathogenic ones, when even the total removal of the neoplasm does not prevent its repeated self-organization. We are able to diagnose dissipathogenic states as long-known pre-cancerous states. Oncological prophylaxis should mainly prevent their appearance, which in the case of cervical cancer stands for prophylaxis of obstetrical hemorrhages and of the shortening of lactation. These events lead to postpartum hypothalamosis, which increases several times the probability of the occurrence of this cancer. Hypothalamosis is an systemic marker, just as an unusual regeneration area or a cytologically detected dysplasia are the local indices of prophylactic management. For example, immunopotentialization of the state of the environment is not only an additional operative management but more and more often should be a sufficient management in the groups of high oncological risk.

From the thermodynamic essence of neoplasm, one can derive some general rules of prophylaxis and therapy which focus primarily on: 1° prevention and treatment of dissipathogenic states, 2° strengthening of the regenerative and defensive mechanisms of the organism and, finally, 3° removal of neoplastic changes as widely as necessary but also as sparingly as possible. For a long time, these rules have been observed in reverse order. That cannot improve the medical outcome, which has not changed for a few dozen years, i.e. recovery depending on the clinical level at the moment of diagnosis. The huge financial expenses have to be concentrated on the first two rules, while limiting them only to the last point is clearly reprehensible. Moreover, doctors who think only in the morphological way should at least understand that the fate of the patient does not depend on the size and localization of the neoplastic changes alone, at least since the Man of the Twentieth Century Albert Einstein in one equation combined mass and energy with the speed of a light. Apparently that fact did not enlighten the enemies of quantum mechanics and thermodynamics in medicine, although they exploit these achievements of the early twentieth-century science whenever they use Internet, computers, CT scanners or just their own cars.

Conclusion

Since 1977 I have not come across any logical argument against thermodynamical theory of natural occurrence of neoplasms not only as the cause of neoplastic diseases but also as the regulator of the proper functioning of the organism, as - by dint of increased dissipation of matter and energy it indicates the areas in the system which have insufficient reparatory-defensive mechanisms. Followers of the other theories are either unable or unwilling to understand that every infection or just a mutation in a gene occur always as a result of stochastically conditioned thermodynamical processes. Those people reject a priori these rudimentary laws of nature, which paradoxically confirm the participation of many different environmental, social, infectious, psychic, and other factors. These factors when considered separately according to the above-mentioned theories should be the only admissible causes of neogenesis. Yet the modern man has long ago understood the naturalness of a thunder even when proverbially striking out of the blue, and therefore he constructs lightning conductors and teaches how to behave during a storm. No person can predict the position of a singular lightening but one can and ought to assess which positions are the most probable. This is a simple and instructive analogy to the neoplasm and precancerous states.

So far, all the theories of carcinogenesis have properly described this event from methodologically different points of view (social, psychological, biological, medical etc). The point is that one should understand the thermodynamical rules underlying each of these approaches [15]. Host organisms are not in a dynamic state of equilibrium with their environment because in such case as open biological systems they could not exchange matter and energy with the environment. On this level of knowledge, quantum thermodynamics combines matter and energy, while technical quantization in a novel way differentiates precancerous states as the host dissipathogenic parts from the neoplasms as newly formed dissipative structures (systems). E.g. tumorigenic action of some hormones differs from their physiologic action because instead of physiological relations there are far-from-equilibrium relations between host Microsystems and cancer. Mutation is only one of a number of internal factors which - like the external ones – may lead any microsystem to the bifurcation point of the unstable internal far-from-equilibrium states. Initiation of the cancer is detectable by MRI'S.

Cancer cells only seem to be immortal, because a priori they are adapted exceptionally to the unique far-from-equilibrium host biological state. It also explains the lack of common denominator for all cancers as well as why do organisms go into senescence and cancer does not? It is because they are two different systems. Cancer can develop only in the host's organism and owing to that they perish together. The sum of entropy production of both systems must always grow.

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