

*ARMEN K. BLBULYAN*  
**LIFE, ENTROPY AND ELIMINATION**

Republican Institute of Reproductive Health, Perinatology, Obstetrics and Gynecology, Armenia  
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*АРМЕН К. БЛБУЛЯН*  
**ЖИЗНЬ, ЭНТРОПИЯ И ЭЛИМИНАЦИЯ**

Республиканский Институт Репродуктивного Здоровья, Перинатологии, Акушерства и  
 Гинекологии, Армения

**РЕЗЮМЕ**

С открытием второго начала термодинамики появилась возможность по-иному подойти к проблемам мироздания, в данном случае – к проблемам организации живой материи. В этом отношении принцип элиминации нашел свое отражение на всех уровнях живой материи, что является не только достижением познания, но и перспективной мотивацией наших действий.

Life is a phenomenon of a cosmological nature, which in its essence has an inner meaning and unconditional expediency. Human body is a sophisticated integral system, where each subsystem is subjected to one common idea. When analyzing every living system, we have to state that without the original concept, it was hardly possible for Nature to work this miracle – create life!

The great Claude Bernard discovered the law of the stable internal environment - certainly the greatest law of that era, which laid the foundation for scientific medicine [17]. Then Walter Cannon develops the concept of homeostasis, which essentially was a refinement of the Claude Bernard's concept [2]. Yet, if Bernard established the rule of the game called life, Cannon offered us the boundaries of what is acceptable. Finally, Hans Selye develops the goal of this game, called adaptation [1]. Selye's doctrine is the most conceptual and maximally generalized. But in order to make better sense of what is going on, let us go back in time a little to the field of physics. Following classical physics, thermodynamics developed rapidly. Two laws of thermodynamics were formulated, of which especially the second turned out to be very fruitful.

What did the second law of thermodynamics give us?

Firstly, the category of energy has become definite and guiding. Secondly, Time has ceased to be a reversible and bare abstraction. It has become irreversible and real. Thirdly, the logic of the development of any spontaneous process was given, where, along with the “arrow of Time”, a new concept came forward – the concept of entropy. It turned out that all processes in space flow with an increase in entropy, i.e., with increasing disorder and chaos. And, finally, fourthly, we came to realize that in this world everything is determined by Energy, directed by Energy and explained by Energy.

The discovery of Second Law of thermodynamics (law of growing entropy) phenomenon of Life in its formation began to be considered as a paradox (Schrödinger and others), i.e., contrary to the law of increment of entropy, the Phenomenon of Life not only does not correspond to this law, but also exists contrary to it [5].

However, the further development of medical science opened up a cascade of mechanisms, at all levels, that ensure the elimination of everything harmful and waste. So, the mechanisms of elimination can be considered as a fundamental mechanism for ensuring negative (at least, minimal) entropy within a living organism, from subcellular to systemic levels of organization of living matter.

A classic example of intracellular elimination is autophagy [16].

Autophagy was originally interpreted as a repair process, during which the „wrong” proteins and other structures had to be resynthesized. The concept of „affected” structures was soon added to this. Finally, in recent years, energy motivation concept has been introduced, i.e., autophagy as a cell response to metabolic stress and replenishment of the energy deficit in order to survive. It turned out that even proapoptotic proteins, caspases, can serve as an energy substrate, thereby preventing cell apoptosis [13].

This can be seen as a deep homeostatic meaning, i.e., the elimination mechanism at the subcellular level ensures cellular stability. As for apoptosis, programmed cell death, no matter how beautifully it is described, it is still a catastrophic process, as a result of which almost all cell structures are eliminated, except for one - tissue factor [3]. The latter, by the way, is a powerful trigger of the hemostatic cascade, which makes this process very mysterious and intriguing.

What links autophagy and apoptosis? This is wastelessness, fine self-regulation and, crucially, the mitochondrial pathway of initiation. And this once again proves the conceptual nature of the existence of mitochondria. There is an assumption that at one time the mitochondrion was a separate autonomous structure (maybe a bacterium), which created a symbiosis with the cell, providing the bioenergetics of the latter [6]. Even the genome of the mitochondria is as “circular” as that of all bacteria and differs from the DNA of the cell.

Finally, the phenomenon of elimination is realized at the system level. These are well-known systems of inflammation, immunity, and hemostasis [8,15]. If the eliminating meaning of the functioning of the first two (inflammation and immunity) is more or less known and perceived, then the logic of the functioning of the hemostasis system has undergone a cardinal transformation in recent years. Moreover, all three systems are very closely interconnected. Immunothrombosis and thromboinflammation are concepts that have been intensively developed in recent years [12]. Firstly, the relationship between thrombosis and immunity, on the one hand, and, on the other hand, thrombosis and inflammation itself contain “revolutionary” elements. Secondly, their interdependence is intriguing, which once again proves the eliminating role of all three mechanisms.

When Giulio Bizzozero discovered platelet, scientific medicine was only taking the first steps towards the knowledge of being [4]. These nuclear-free fragments of megakaryocytes are found everywhere and in high concentrations ( $150\text{--}400 \times 10^9$  cells per liter of blood, which is several times more than leukocytes). Due to the secretion of oxidants and antimicrobial proteins (thrombocidin, defensin, kinocidin), platelets play a pathogen-eliminating role [20].

By the way, the charge of these proteins is opposite to the charge of the bacterial membrane, which greatly facilitates their activity. Thanks to the receptor system (including Toll-like, Fc receptors), platelets perform an antigen-presenting role, being the first link in natural immunity [11].

Chemokines produced by platelets initiate neutrophils, monocytes, and other active elimination cells. In the light of new data, the value of fibrin has also been revised; in particular, fibrin is presented as a “guillotine platform” for the pathogenic factor. Fibrinogen limits the spread of the pathogen, providing a direct antimicrobial effect, and also activates innate immunity cells through integrin- $\beta 2$ . Experimental mouse models lacking fibrinogen died very quickly from sepsis when they encountered a pathogen [7].

Platelets in their structure are the most stable element in this hierarchy of elimination mechanisms. And in order to be activated they require the initiation of a number of signaling systems - from the endothelium to the same neutrophils and monocytes. It gives the impression of a sequence of reactions of these systems. It should be emphasized that the entire elimination system basically has two initiating factors: damage-associated molecular patterns (DAMPs) and pathogen-associated molecular patterns (PAMPs). Thus, the pathogenetic mechanisms of initiation are of a general biological nature, extremely generalized and concise [9,14,18,19]. And if the reactions of the inflammatory and immune series in their internal dynamics are reversible and regulated, then the reactions of the hemostatic series are apparently phylogenetically (possibly ontogenetically) more ancient and irreversible. Apparently, this is the reason for the catastrophic nature of the latter.

It is necessary to distinguish three concepts in modern hemostasiology - coagulopathy, thrombophilia and thrombosis. Both situationally and prognostically, all three differ, which is very important from the point of view of an optimal and differentiated approach to them.

By the way, COVID-19 has shown once again that the depletion of inflammation and immunity systems leads to a crisis in the hemostasis system with all the consequences. COVID-19 “revealed” another elimination component - the REDOX system. The uniqueness of the REDOX elimination system lies in the fact that, unlike all the others, it originated about 2.5 billion years ago, after the so-called oxygen “holocaust” [10]. One of the components of the REDOX system is ferritin, a sharp increase in which in

the blood of patients is a poor prognostic sign. So, the entropy led to life architectonics' development and formed the goal as "antientropic" phenomenon.

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SUMMARY

With the discovery of the second law of thermodynamics, it became possible to approach the issues of the universe in a different way, in this case – to the issues related to organization of living matter. In this respect, the principle of elimination has been reflected at all levels of living matter being not only the achievement in cognition, but also a prospective motivation for our actions.

**Keywords:** hemostasis, PLT, second law of thermodynamics, elimination.

არმენ კ. ბულბულიანი  
ცხოვრება, ენტროპია და ელიმინაცია  
რეპროდუქციული ჯანმრთელობის, პერინატოლოგიის, მეანობა და გინეკოლოგიის  
რესპუბლიკური ინსტიტუტი, სომხეთი

რეზიუმე

თერმოდინამიკის მეორე კანონის აღმოჩენით, შესაძლებელი გახდა სამყაროს საკითხებს სხვაგვარად დანახვა, ცხოვრების ორგანიზებასთან დაკავშირებულ საკითხებთან მიმართებაში. ამ თვალსაზრისით, ელიმინაციის პრინციპი აისახა ცხოვრების ყველა დონეზე, როგორც არამხოლოდ შემეცნების მიღწევა, არამედ ჩვენი ქმედებების პერსპექტიული მოტივაცია.

