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"The Chronics" within the context of fundamental biology

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The problem of chronic diseases is analyzed from the perspective of general biology. We develop and substantiate the idea that the chronic diseases are an evolutionary mechanism of cleansing the population and the species of its mutational load. This is achieved by keeping self-restoration systems of a chronically damaged organism in the off-state, unlike in the 'permissible' self-restoration triggered by the acute damage. Evolutionary, chronic diseases serve as a somatic marker for the accelerated elimination of their carriers.

Keywords: chronic diseases, evolution, self-restoration systems

The fundamental problems and arising critical questions often originate from the specific "evident" experimental data. An obvious example is the phenomenon, usually manifested as a persistent, incurable, chronic pathology, which is informally called "the chronics". There are numerous actual manifestations of the chronics, but in total they indicate the existence of a specific phenomenon. The chronics, being an object of a treatment in practice, have some common basis regardless of its various manifestations The fundamental question – "what are the chronics" has arisen on the wave of a rapidly developing novel biomedical technology – cell therapy.

The idea of using stem cells (SC) as a special therapeutic approach has a long history. However, after obtaining the human embryonic cells in culture, the rapid implementations of this idea started as absolutely obvious trend in medicine which does not require any additional justification. Indeed, if SC are the universal source of everything self-replaced and self-restored in the organism, they may repair any damage and restore the norm. Thus, cell therapy is developing on the basis of trend that SC in the organism are the universal source of self-restoration [1]. On the other hand, if any organism (except for the ones, completely poisoned by chemotherapy or radiation) has its own SC why there is no self-restoration in case of the chronics? If your own SC do not cure you for some reason, why would analogical, introduced from outside and used to treat any damage, actually treat this damage? Why would SC, introduced from

outside, are active at chronic pathologies, if your own ones are not efficient? And in fact, SC introduced from outside are very often helpful, like therapeutic means. There is some obvious contradiction, some incongruity. Every tissue, every organ, and every vessel has its own mesenchymal SC (MSC) "on duty", which are ready to act at any moment [2, 3]. Both mesenchymal and hematopoietic SC (CD 34) circulate in blood constantly. Their concentration is not high but stable. This may happen only in case of equilibrium processes – some cells are gone (get used, perish, *etc.*) and the same portion of new ones comes in. The number of SC passing through some conventional cross-section (of a vessel, a damaged tissue, or an organ) over 24 hours is larger than that in the bone marrow. The number, constantly circulating in blood, is some potential "self-therapeutic" amount of SC "on duty". However, in case of a long-term inveterate chronic disease, its terminal stage, SC do not enter blood at all. At the same time, they are in their depots, niches, in such numbers which would be sufficient to self-cure any disorder in the organism. In case of a stable chronic disease they do not penetrate into the pathological tissue (organ), but even if they do pass through it, they do not remain there, just circulate . Why then the therapeutic effect of the introduction of SC from outside would be expected? Usually an even stranger technology (from the standpoint of logic) is applied, like introduction to patient of his own autologous SC, often extracted from his bone marrow. These are the same SC which did not act in the organism, although they were present. So why is the therapeutic effect anticipated? How would it possibly come? Still, the effect is observed indeed – permanent for some events, and temporary for others [4]. Foreign (allogeneic) SC act as therapeutic agents, not worse than the patient's autologous ones [5, 6].

These are key questions, the answers to which may promote a proper treatment technology using stem cells. To answer this question, it is worth to consider the normal SC behavior when they ensure self-cure and self-restoration. This happens at all kinds of acute injuries – traumas, mechanic damages, burns, and acute poisoning, *etc.*

In case of sudden injuries an individual dies from fatal traumas fast or gets restored if traumas are compatible with life. In principle, the same is true for infectious diseases, poisoning, *etc.* However, everything is different for the chronic pathologies. The chronics are a damage of a different type in its very essence [7].

Basically, the chronics as a special state of the organism are far beyond the framework of medicine and should be considered and analyzed as a general biological phenomenon, because a human being is a living organism, not principally different up to the last molecule from the rest of living beings. All human pathologies are disorders, to which a human organism reacts biologically like all the living beings in nature whereas medicine is the sphere of activities, impacting the living organisms beyond the framework of nature. Medicine is a product of the human intellect, some unnatural phenomenon. Still a human being is a living organism, a biological object, living and reacting to everything as a Biosphere constituent, an absolutely biological object, determined by the mechanisms of life and subject to the life laws.

Life on the Earth exists as a phenomenon in the form of "self-" information in the pro-

cess of evolution. It is realized via reading the information, defined by the general term heredity. Notably, the destruction or impairment of heredity brings to death. According to the concept of information entropy the randomization of information takes place in nature constantly, everywhere and with no alternative. Due to chaotically accidental events the information may transform into "noise". Consequently, the entropy pressure, acting constantly, results in the randomization of genetic information, which is manifested in the living beings as changes in the material carrier of heredity, known as mutations. Therefore, mutations are some kind of the entropy expression in the sphere of living nature. To save life there should be radical resistance to the unceasing randomization of genetic information [9, 8].

Mutations predominantly worsen the heredity as vital information, so the living organisms have special mechanisms to preserve it. Inside the cell, there are systems, protecting against the penetration of the agents, which could reach the genome and destroy it, in particular, the reparation systems. At the level of the organism, this is elimination of damaged, "suspicious" cells. However, in any perfection, it is impossible to eliminate absolutely the randomization consequences in closed systems – a definite cell or a definite organism because of fundamental limitations of the informational closedness. Inside the organism the randomization of phenotype-determining information of a specific cell ends with this very cell, as all cells in the organism have a limited period of individual existence. The danger of information randomization for life is related to the generative line. The filters, removing the mutated cells, are numerous, and highly effective but entropy as an obligatory attributes of nature impacts everything in the full volume and with no alternatives. Therefore, albeit negligibly rarely, the informational randomization in the generative line occurs as the impairment of genetic information, namely appearance of mutations.

The living beings have a special mechanism to fight randomization radically for elimination of the impacted information. For life to exist on the Earth a radical fight with randomization is implemented in a form of the multiplication mechanism with a high degree of redundancy and further elimination according to the Darwinian selection. The reproductive redundancy is one of the mandatory constituents of evolution and the very possibility of life existence. Thus, the reproductive redundancy in combination with Darwinian selection ("the survival of the most adapted ones") does not allow life to degenerate under constant and very powerful entropy-determined mutation pressure.

The number of individuals, living in any area, community, continent, in any space of the planet of Earth, is highly stable within the thresholds of natural fluctuations. It is reproduced constantly and ubiquitously on a larger scale compared to stable existence. The mentioned difference is constantly and ubiquitously eliminated down to the number of stability.

Actually, the redundancy of reproduction is often presented in literature as some kind of a paradox. Popular literature lists arithmetic calculations as follows, in ten years one dandelion plant could occupy the whole solid surface of the Earth; one cod couple could replenish all the seas and oceans of the planet with their offspring, *etc.* It is considered quite adequately in serious works, but only in the terms of

dispersal of organisms (mainly within their own ecological niches). The redundancy of offspring is analyzed from the standpoint of random occurrence in the conditions, allowing for their existence, to "hang on" in any place, where they could survive. Even if almost all the reproduced ones perish, those who "hang on" will grow; give their redundant offspring, which will do the same, *etc.* Surely this element of ecology, using excessive reproduction, occurs. However, only the healthiest, viable offspring can "hang on" and exist long enough to reproduce. As for weak offspring, without any full-scale genetic potential for adaptation in the wide range of external conditions but often with the pressure of neighbors, it will perish before the reproduction. Thus, the redundancy of reproduction ensures the continuity of existence only for those, who, due to their possibilities, have managed to "hang on" and then withstand the pressure of surrounding conditions and to give some offspring. The phenotype, capable of ensuring all this, is the realization of a robust genotype. The genotype and consequently phenotype weakening of any individual increases the possibility of eliminating the latter. This is the way the species, populations and Biosphere in total keep the information (heredity) preserved in conditions of constant and ubiquitous entropy as mutational pressure.

However, if a mutation is useful, it is not just randomization, it is improvement. As for the chronic disease a change of phenotype for the worse is a marker for elimination. Principally, the chronics, as a continuously existing non-repairable and progressing damage or disorder of an organism, are a specific phenotypic manifestation of biological inadequacy. This is revealing changes in the status of a relevant gene or several genes – mutations, recombinations, unfavorable combination of polymorphic alleles, translocations, *etc.*

Any chronic is naturally implemented as follows.

A too long-run infectious disease may be a result of a mutation, acting on the immune system.

A too long-term weakening of the organism due to some natural poisoning is "suspicious" for a mutation in the detoxication or reparation system.

A too long non-recovery from a trauma is "suspicious" for a mutation in the self-recovery system.

In fact, any chronic suggests the existence of a harmful mutation.

For the existence of life, everything that is weakened for any reason and cannot self-restore quickly is a subject to absolutely uncompromising elimination. In nature, the organism must self-repair any acute injury as fast as possible otherwise may be eliminated. The chronics as a marker of elimination cannot exist in the form of a long-term status of the organism. However, in nature, it is possible to remove the chronics only together with its owner. This carrier of the dangerous genes should vanish to preserve the population, species, and life as such. Therefore, the chronics are not envisaged by life as a long-term state of the living being, and the mechanisms of its self-cure in nature do not and even should not exist. Such mechanisms, masking the harmful mutations, thus strengthening the mutational burden, would be harmful to life.

Generally, elimination is one of the central processes of supporting and ensuring life. In

the organism, these are targeted and programmed processes. Damaged macromolecules and organelles are eliminated in cells [10]. At the cellular level, the outside or inside induced self-elimination in the form of apoptosis is studied in detail [11, 12]. The process of intra organism removal of "suspicious" cells is diverse. In addition to apoptosis, there are necroptosis, pyroptosis, *etc.* [13, 15, and 14]. One more very interesting mechanism of cell elimination in the organism has been recently described. It is realized via special markers – "eat me" – which appear in potentially dangerous cells [16]. White blood cells destroy such cells due to this marker.

As mentioned above the chronics are a marker of elimination at the organism level in natural conditions. This is explained by the fact that during all the billions of years of evolution, in nature the damage of the organism could be induced only outwardly, in the form of mechanic traumas, acute poisoning with factors of instantaneous effect (poisonous plants, bites of venomous insects, poisoning with products of bacteria in spoiled food, *etc.*) or infections. All these injuries were either self-removed quickly or, if the process of recovery and cure was delayed, the organism became disabled and vanished quickly as well. The chronic could occur only due to some internal processes, inadequate (procrastinated) restoration of damages, which were the results of genetic deficiency. Everyone with a hint of any chronic carried a marker in the form of changes in physical and metabolic possibilities of an individual. The heredity of such disorders became hazardous for the species, the population, and life. Any impairment of the genome, which reflected negatively on the adequacy of its owner, became the step of genetic inadequacy, leading to the degeneration of the living being at every level – the population, the species, and integral taxon. To prevent the degeneration of life as a phenomenon in its Biosphere form, the program of eliminating the carriers of the chronics gets turned on and it is targeted at accelerating this terminal process at the individual level for the termination not to expand on a large scale. But while fighting for its existence, life as a phenomenon not only formed the mechanism of withstanding entropy, but also transformed it into the factor of its own perfection. .

If the mutation is found to be useful, the direction of the selection – which is adapted more and who is less – changes. However, the mutants with a new useful feature are rare in the population. The rest which becomes less adapted compared to the useful mutant constitute the main bulk of the population (species). Thus, the selection by this selective marker starts working against them. A lot of people even now consider this process of gradual selective replacement of the remaining individuals of the population (species) with useful mutants to be the basis of evolution. Nevertheless, this process is rather slow and long-term. The evolution has already been going on for 4 billion years. As for the chronics, their owner (a single one) is subjected to not just selective pressure of the whole healthy population, but some universal ensuring of elimination. It is universal because such individual transfers to another status – the chronics, i.e. to such metabolism which evokes the strengthening, increasing the probability of abolition under the impact of the entire environment with both living and non-living natu-

ral factors. Maximally fast elimination of such individuals in nature is required to have no genetically "apprehensive" offspring in the population

To accelerate the elimination of any "apprehensive" individuals, the relevant mechanisms were formed in the whole living world in evolution as a basis of the integral law of life – preservation of heredity. Human civilization has produced numerous unnatural agents causing the chronics [17] along with the care system for those suffering from the chronics (social conditions, medicine, legislative norms, *etc.*). It leads to constant presence and accumulation of impairments and damages, not removed via self-restoration, in the population. And the next question, which should be asked for complete understanding, is – how, due to which reasons and processes can the chronics exist in the conditions of human civilization?

There are two extreme opposed variants and some overlapping of them. One variant is an intensely manifested hereditary disease. It is connected initially with the mutation, leading to the impairment of a structure, encoded by this gene, or a function of its product e.g. the absence or deficiency of peptide hormone, metabolism enzyme, nuclear lamella, *etc.* The organism often, although not always, can temporarily compensate these defects via enhancement of other functions, but the restoration systems of the organism cannot help much in this case. Another variant is related to a continuous external impact of high doses of poisonous substances in water, air, and food, which exhaust the systems of protection and restoration. There comes a moment when there are not enough possibilities for their detoxication up to the unrepairable destruction of the organism, i.e. accumulation of damaged proteins, increasing deficiency of coordination of the metabolic cycles and enzymatic chains, insufficient reparation of nucleic acids, *etc.* However, there may be a single external impact irreversibly destroying the system of protection and restoration, leading to the chronic impairments. A typical example is radiation (200 REM – and the chronics is guaranteed). In this case all basic systems of the organism are impaired. The occurrence of a chronic impairment is more frequent in the case of combination of internal and external factors. An external factor is a constant impact of a hazardous factor in seemingly "small" dose and the internal factor is the hereditary disposition of an organism when some changes in a gene (or several genes), caused a decrease in the product function, for instance, in the detoxification enzymes activity [18]. If there was no a toxic agent, deactivated by this enzyme, the weakened function of the latter would be sufficient to ensure normal course of the process. On the contrary, rather often the damaging substance which should be transferred into the harmless form came to the organism in the amounts insignificant for the normal detoxification system, but this dose exceeds the protective possibilities of the system weakened by a hereditary defect. In this case the damaging factor cannot be neutralized and it works all the time (Fig. 1). The invented prior to the chronic impairments abolish the general, integral systems of restoration including stem cells. If the influx of hazardous factors is constant, the protection systems get exhausted and the chronics occur.

The chronics, if it is not a classic hereditary pathology with intense early manifestation,

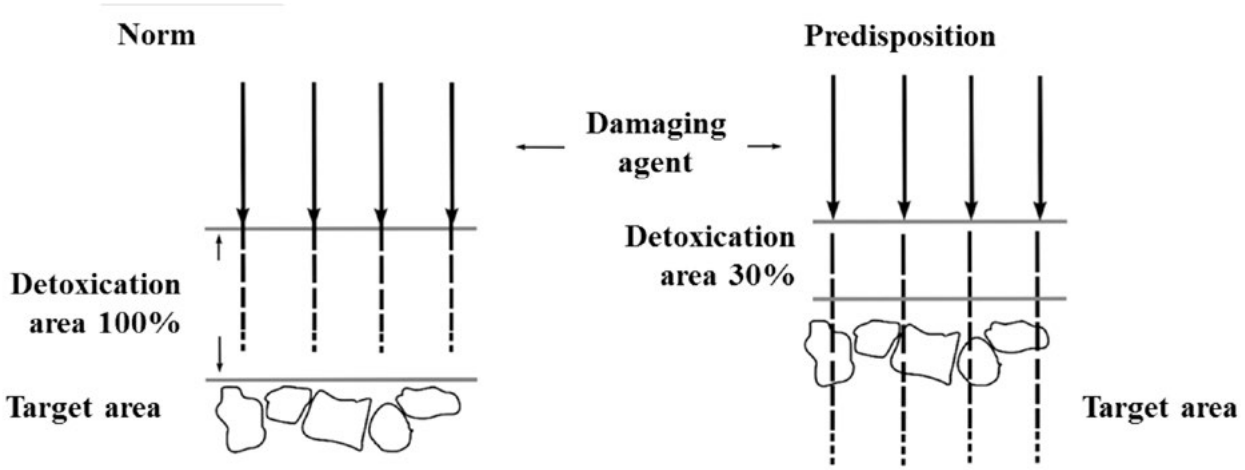

Fig. 1. Hereditary perdisposition, implemented by the potency of the damaging factor

When the protection reserves fall below the potency of the toxic agent, constant destruction of targets by the latter, requires the increased activity of restoration systems. Their exhaustion leads to the initiation of the chronics.

usually develop with aging, appearing in the middle and older age categories. This specificity of chronic diseases is explained with the classics of life – the changes in functions (qualitative and quantitative ones) during ontogenesis. Considering various situations in the course of evolution, all the organisms have formed some preservation of functions. In the most generalized form it is usually believed that such preservation is about ten-fold.

Thus, until the reserves decrease by 90 % the organism is phenotypically healthy. However, if there is any genetic predisposition, the organism does not have its full normal reserve, those 100 %, which define ten-fold preservation [19]. With age, the reserves drop in accordance with the time course. So, the chronics are actually a result of two factors – the remaining preservation and the potency of the toxic factor, which is neutralized by this specific function of the organism. However, in reality, the function is usually organized in a complicated way and the potency of the toxic factor is also multi-dependent (the permeability degree for the target cells, a total number of the incoming damaging agents, the index of income continuity, the toxicity level, *etc.*). In the "accomplished" form it results in generalized specificity of the factor, the time of its continuous income from one side and the level of remaining preservation function from the other side (Fig. 2). All this is implemented for each individual particularly, due to the specificities of genetic impairments: either systemic ones concerning the housekeeping gene in all the cells of the organism or in a specific organ (tissue) as a "weak mutation" of the organ-specific gene – a leading pathology. By this chain of processes the defect of any gene (predisposition) is implemented as an elimination marker. For faster elimination of the deficiency carrier the acceleration mechanism evolved– the restoration systems cease functioning, partially or completely. This is ex-

actly a cause of the chronics. This was experimentally proven for patients with the terminal stage of damaging different organs – the stem cells circulated in the blood flow but did not go to the disease foci [20]. The chronics as a variant of long-term state were not "prophesied" by nature for the living beings. The specificity of this variant lies in the fact that when one life subject has a predisposition, the rest ones, not predisposed to a small amount of a toxic agent, are stable. Therefore, the chronics seem to start suddenly for no reason at all only in the owner of the whereas other people, living close, do not suffer it. In this case, a behavior of the patient's own SC differs from that during a sudden trauma, acute poisoning or infection. The mechanism of resistance to the information randomization created in the course of evolution turns off the SC activity towards restoring the damage.

Starting a specific stage of the damage, the chronics will not disappear even if the toxic agent has been removed and a special chronic, self-supporting pathological state of organism develops.

This is a fundamental conclusion: the chronics as a state of life are unnatural for life as a phenomenon and the living being does not have any mechanisms of self-curing it, Instead, the alternative pathological state, evolutionary

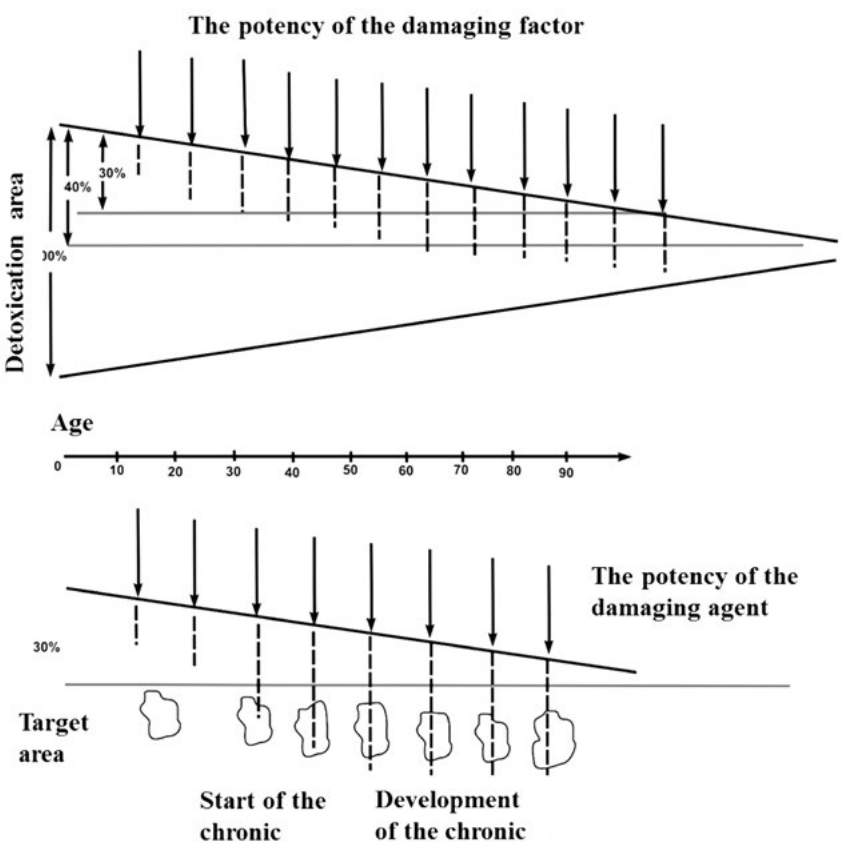

Fig. 2. Age-impleneted hereditary predisposition

The age-related decrease in the potency of protection systems eradicates their reserves, naturally present in norm. With the initially weak protection function, the reserves, being eliminated with age, are insufficient to remove the damaging factor. The chronics start and develop. The fewer these reserves are, the sooner the chronics start, and the faster and the harder they develop.

formed as a marker of accelerated elimination, advances.

The chronics may serve as a good example of fundamental differences between Nature and Socium, which so often are not seen, not analyzed, and not considered. In Nature, the chronics are a transitory state, progressing with the purpose of sooner elimination of its owner. It is a marker of biological unreliability and at the same time – one of the mechanisms of sooner removal of its carrier. Instead, in Socium, the chronic disease is a motive of accentuated attention and measures to preserve the chronic carrier. In Nature, biological inadequacy is a subject to sooner and radical elimination using all the possible ways of Biosphere. In Socium, the owners of all the kinds of pathology are subjects to preservation and special care and support. In Nature, biological laws are executed strictly and highly effectively, whereas Socium blocks them to the extent of its possibilities.

A practical conclusion of this fundamental course is a relevant task of fundamental biotechnology: to find such solutions, which would provide for natural processes of self-cure in combination with biotechnological ones, to be sufficient and adequate to restore the alternative state of restoration systems from the chronics one back to the norm. In other words it is necessary to elaborate the biotechnological approaches which would transfer the chronics from the marker for elimination into the target for his own, this time active, systems of self-cure and self-restoration.

The very fact of the occurrence of the chronics is in itself a strong proof that for some reason the natural mechanisms of self-preservation of the organism, including all its stem cells, do not function or are not effective enough. Thus, the chronics should be dealt with as soon as possible, but it would be even better to remove them during the latent period or, ideally, not to let it happen at all. Here SC should be used with the consideration of individual features, in combination with the knowledge of "weak points" of each individual, i.e. precise predispositions and the lifestyle, which would provide for preventing the impact of his predispositions.

Yet, there are no substantiated technologies to prevent the occurrence of the chronics in case of genetic predisposition, just some general notions in the terms of SC usage. Meanwhile, many people have the chronics and it is necessary to find satisfactory ways of removing it using the possibilities of cell therapy.

The fundamental features of the chronics and the available experimental and literature data may be used to formulate the generalized notions on potential therapeutic activity of SC, first of all mesenchymal ones (MSC), in case of chronic pathologies. It would require at least a general idea of why MSC, present in a chronically ill organism, along with the rest of SC, do not act, do not self-cure the chronics, but once injected from outside are able to cure it, in some cases even radically.

The possibilities of the organism regarding self-preservation and self-restoration are unique. If something does not function in it, there are special reasons. The chronic impairments develop for a long time if no fast and radical solutions are undertaken, like removal of the damage and restoration or destruction of the organ, tissue and death. Long-term

course of the process *de facto* testifies to the existence of some mechanisms, ensuring, preserving, and supporting the state which we view as pathology and the whole analysis of reasons is limited with the notion only – "the organism feels bad", the specific frames being merely where, in what way and how bad it is. If we leave the frames of a specific organism as such, as an individual, the situation looks quite different. Though a human to the last molecule is a living being just like all the others the intellect excluded it from the Darwinian selection. And non-repairable impairments have become continuously existing chronics. While in Nature, this state is very short, vanishing fast via the elimination of its carrier, in Socium it exists as a long-term transitory "sick" state. Consequently, the chronics and the norm, being unique for each individual, are different, rather stable self-supporting states, performing principally diverse biological functions. At norm, any acute damage switches on the self-restoration program, one of which is the formation of SC out of progenitors and their active functioning. This has been well-studied and strictly documented. MSC were isolated from the blood of people with heavy traumas and multiple damages and cultivated in the medium. They were actively penetrating blood just after the trauma as a reaction to it, while in the blood of healthy people they were present in small amounts or could be not found at all [20]. But this happens only for natural processes in case of acute damages.

As for the chronics, the capability of SC formation and migration decreases along with an increase in the number of risk factors, practically with the pressure of pathological factors [21]. In case of acute traumas, MSC are not just activated in response to the emerging acute inflammation, they are actively moving towards the the damage zone [22].

If the damage is not restored soon and the destruction comes to the stage when the organism becomes phenotypically inadequate for a long time, the mechanism of alternative state is turned on, the biological essence of which is to accelerate the elimination of the organism. And one of the elements of the acceleration of its elimination is turning off the SC functions that has been well registered as well. No MSC were found in the blood of patients at the terminal stage of the chronic damage to kidneys, liver, or hear [20] but they were present in their niches, in the localization zones of the internal walls of vessels. These alternative states of SC were *de facto* revealed and at the next stage the idea of what these alternative states are, which mechanisms they employ for self-support, has been developed. As an organism is a single whole, the turn to the alternative state, leading in nature to the accelerated elimination, is also systemic.

The first indication of such a turn is the state of the zone of ingenuous chronic manifestation, particular tissue or organ. The systemic factor, the general organism background leading to this turn and its support is the chronic, sluggish inflammation. It is insufficient to trigger alarm signals, but working constantly it mitigates and exhausts the signaling of SC mobilization and activation. At some stage of development, in the zone of the chronics occurrence some damaged cells stop (or may be, do not even start) producing an alarm signal, i.e. a set of signaling molecules including cytokines, chemokines, growth factors, microvesicles of specific composition , *etc.*. Some of

these are already known. The scientific literature has shown such factors of stem cell mobilization as granulocyte-stimulatory growth factor, SDF1, substance P, adhesion factors, *etc.* [23; 24; 25; 26]. The signaling molecules with such functions activate stem cells (both hematopoietic SC, and MSC) and direct to the necessary sites. There is a wide pattern of alarm signals, which are formed in case of acute damage [27] but their composition and number change at the chronics. The phenomenology of this state has been defined already. The double label was used to prove that after MSC were externally introduced to mice with simulated renal ischemia, they were not found in the damage zone at all, although the therapeutic effect was registered [28]. The introduced MSC "did not see" the damage zone and did not move to it. The patient's own SC circulating in blood as "on duty" agents do not see the chronic damage either. Only a massive injection of MSC caused systemic therapeutic effect, potentially inherent to them due to a universal set of signaling, trophic, and restoring macromolecules.

These date demonstrate once more that at the chronics the status of self-restoration systems turns from active into passive one. And only the external impact may change the situation. As for turning mechanisms, they are multifactor and are studied intensely.

At first it was discovered that in case of standardized cultivation in culture, MSC are highly identical but the identity vanished with the variation of conditions. After the imitation of impacts, present in the organism in case of various damages, two extreme states were described which served as a basis to introduce the notion of "MSC polarization" [29, 30]. In one extreme state, as described before and is still being thought now, MSC have immunosuppressing properties whereas in the other state they have opposite, proinflammatory effect. In both states their properties and physiological functions, the proteome composition, and biological properties differ radically [29, 31]. However, by now all these changes are studied almost exclusively in the *in vitro* systems. The *in vitro* conditions are far from being identical; each investigator has his own impact protocols, natural sources of MSC, lines of animals, the rarely obtained human samples *etc.* Therefore, the results presented vary and often are quite contradictory, which makes impossible correct generalization. Nevertheless, the main conclusion of these investigations is already obvious that in the organism MSC change their properties "to match the task" needed for the organism in the given case. Nevertheless, the organism was formed in the process of evolution and during all those four billion years, the central task of life as a phenomenon was fighting randomization of the information. The species whose individuals did not fulfill this task vanished due to the mutational pressure. The elimination of mutants required the chronic to become a target, a marker of elimination. And this central task of life as a phenomenon still remains the same for human as a biological object. That is why MSC become inactive in case of the chronic disease. The mechanisms of such rearrangement have not been studied yet, and it is unknown which molecular processes change for this purpose. There are intense studies on the MSC transfer to various restoring or aggressive states, and interaction with other cells but inactive MSC are not in the focus of researchers.

The first remote ideas of the phenomenology of transferring MSC into the inactive state in case of the chronics are described in the form of the chronics itself. At the chronics SC and their progenitors lack the ability for mobilization and reconstruction "to match the task"; there is only chronic inflammation – continuous and smoldering. It is not capable of triggering the activation of protection systems, it is "weak". However, it acts continuously as a constant irritant for these systems. Some time later, natural processes of adaptation turn off the perception signaling of the alarm systems. The first and foremost fundamental task in fighting the chronics is to find out b in what specific way it occurs, and how it can be restored.

The situation with switching between states for other kinds of cells is studied better. Switching between states of cells and tissues is a universal phenomenon, pertaining to the whole organism. First of all, it became clear regarding the immune system cells. All the systems cooperate in the organism, and their functions are mutually overlapping. A role of the immune system goes very far beyond the framework of the term "immune". Leukocytes interact closely with the restoration system in general, including stem cells, and the functions of some groups of leukocytes and stem cells overlap. It is especially evident for macrophages, which are highly heterogeneous in their functions and origin.

Embryonic macrophages, originating from the yoke sac endoderm, do not pass the stage of monocytes, but differentiate directly into specialized tissue macrophages. Hematopoietic progenitor cells appear later and compose the second wave [32].

As the origin of macrophages is double-natured – from the yoke sac (cells of brain microglia, subcutaneous Langerhans cells, Kupffer cells, *etc.* [32]) and from hematopoietic cells of the bone marrow, it makes them the candidates for manifestation of varying properties [33]. This is a self-reproducible system of cell populations which do not have any special "stem" predecessors. After birth, macrophages are present in all the organs, constituting 10–20 % of all the tissue cells in some of them (Kupffer cells could serve as an example).

Macrophages, formed from the stem cells of bone marrow, may be in special functional states. The examples to such alternatives may be found in M1 and M2 macrophages. M1 is considered to be the main state, characterized by the release of proinflammatory cytokines and ensuring the protection and elimination of dangerous objects (bacteria, tumor cells, *etc.*). M2 state, the alternative one, is characterized by the release of anti-inflammatory cytokines and factors, promoting the regeneration of tissues, which ensures the restoration from damage and repair stimulation [34]. These states are switched on and over to one another via the set of their signaling molecules: M1↔M2. In the norm, this switching promotes self-restoration from damage if the change of alternative states is violated, M1 macrophages will start destroying what is necessary for the organism, whereas M2 will stimulate the tumor, restoring and protecting against elimination. Tumors recruit macrophages into their stroma, switching them from the main state M1 to the alternative one – M2. Being in M2 status, macrophages stimulate, support and even protect the tumor.

The understanding of nature of the alternative states came due to the research on tumors because the cancerogenesis is not the just adaptation of metabolism to the alteration of environmental conditions but a quasi-stable self-supporting state, resistant to short-term fluctuations and changes in environmental conditions. Nevertheless, the alternative states were first studied in the cells capable to migrate and actively move, macrophages, since they are the most vivid example of the alternativeness and provide the most convenient methodological possibilities.

Macrophages dynamically change in the course of different phases of wound healing. M1-polarized macrophages mediate the damage of tissues and initiate the inflammatory process in response to it. At healing, during the early stage of repair the infiltrating macrophages expressed M2 phenotype and their exhaustion inhibited vascularization, cell granulation of tissue and scarring [35]. In the peritoneal model of inflammation the macrophages in the resolution phase were presented as a unique mixture of M1/M2 phenotypes, where the presence of the sufficient amount of cAMP limited the activity of M1 [36]. In case of the spinal cord damage, MSC transplantation to the harmed zone results in an increase of M2 and a decrease of M1 [37].In the model of acute ischemia of heart and kidneys, monocytes were recruited into the tissue and their activated status and dynamically changed from the predomination of M1 to the predomination of M2 phenotype [33].

Alternative states are caused by a complex of conditions, the status of the organism, tissues, and serve as a response to such conditions. Having arisen and switched into different alternative state, macrophages start impacting it actively.

The direct and indirect effects of macrophages on the restoration processes as well as their status are closely connected with the restoration stages. During the post-inflammation phase of reparation, the exhaustion of the pool of macrophages in the damaged tissue leads to severe hemorrhage in the damaged organ and the termination of restoration. And the exhaustion of myeloid cells at the early stage of reparation (the inflammatory phase) reduces the formation of vessels considerably along with the inhibition of epithelization. But the exhaustion of macrophages at the late stage of reparation, cell maturity, does not impact the restoration process any more. It proves that the role of macrophages is relevant at early and initial stages of restoration and is no longer significant during a final process[38].

Polarization of solid tissue cells has been demonstrated for adipocytes. They may also be either in the state, blocking inflammatory processes, or in a different state, releasing proflammatory cytokines and stimulating inflammatory processes [39, 40].

Because the organism is a unified system, all its cells and tissues interact and their norm is a mutually supported and mutually coordinated, state. As for tissues, i.e. complex and multicellular structures, alternative states of specific cell types may integrate into alternative state of tissues in case of acute damages. It may occur in the form of a “need” signal and lead to the compensatory state as a restoration stage. Here a strong external impact – local or systemic damage – requires a transfer into a different state to restore the norm. But

there is no norm; it has been destroyed by the trauma. It has to be self-cured, the damage should be repaired. This requires passing into a different alternative state and then coming back to the normal one.

However, this happens in case of the acute damages only. There is no switching back to the norm in case of the chronics. In a patient with chronic venous ulcer there are no processes, eliminating chronic inflammation. And there is no switching of macrophages from M1 to M2 in the damage zone [41]. There is a self-supporting pathological state, the preservation of which involves active participation of macrophages and there is no self-restoration. This is a vivid example of the way in which macrophages actively participate in both pathological and restoring processes.

These processes are described for different tissues at the various impairments. An example is the cell system described rather in detail for the adipose tissue – adipocytes, adjacent macrophages, MSC and their progenitors located in these tissues. In normal conditions, adipocytes release biologically active substances, such as lectin and adiponectin, which promote sensitivity to insulin. Adipose tissue fulfills the complicated function far beyond the framework of reserves. When this tissue is in the norm the main part of the macrophage is in M2 status, stimulating the repair processes and blocking a possibility of the inflammatory reaction. This is a kind of a self-supporting state of the norm.

Macrophages of adipose tissue of slim mice secrete the cytokines of antiinflammatory profile that a powerful factor of preserving the norm of the tissue and the organism as a whole. However, at adiposis, adipocytes release proinflammatory factors, which induce recruiting and activation of adipose tissue macrophages into M1 status. Gradually, via the release of proinflammatory cytokines, they activate the whole inflammatory chain of processes, blocking the action of insulin, which leads to the insulin resistance. Thus, during adiposis, macrophages pass into the alternative state M1, release proinflammatory cytokines, and this time participate in the systemic chronic inflammation of the whole organism [40]. The self-supporting pathology starts, which leads to the alternative transfer of all the adipose tissue constituents into the pathological state. The result is the complete switching of signaling chains and biological processes, leading to the stable self-supporting alternative pathological state of the tissue [42]. This is achieved by transfer of all the systems, which should participate in self-restoration in the whole organism (and not only in chronically inflamed tissue), into the chronics, i.e. inactive state. In the organism a gradual alternative switching of cells, interacting with macrophages, occurs with their active participation. The arising self-supporting process, implementing M1 phenotype of macrophages, turns off the self-restoring activity of MSC [43].

Actively migrating cells of the immune system plays a key role in the state of the organism. They may move to any tissues, organs, interact with each other and with cells of other tissues. In addition to the mediated impact, they also modify the MSC activity via direct contacts and a special spectrum of signaling molecules. The impact of macrophages on MSC changes significantly the biology of the latter. Therefore, the researchers write not about impact, but rather about macrophage-

induced MSC phenotype with its special spectrum of cytokines [44]. But the relations of MSC and macrophages are mutual. The impact of MSC on macrophages is no less significant. A new type of macrophages has been described, which is formed due to co-cultivation with MSC. These are "MSC-taught macrophages" which are assumed to be a new type of alternative macrophages with a considerable potential of tissue restoration [45].

The significance of alternative states, evaluated in the general form, seems to be clear. These states occur at the norm in response to the "need signals" which promote the appearance of a quasi-stable source of the signaling, trophic, structural macromolecules, transferring the surrounding tissue cells into the stable state required in the acute, often critical and highly dynamic conditions. At the norm, this is a transition to the status of keeping self-preservation and self-restoration.

But all these states, transitions, the interaction of cells with each other may lead to the situation when the irreparable damage or impairment transfer the self-cure systems into alternative states, not able to correct or regenerate. The result is development of the chronics which is a marker for elimination of this individual in wild nature or for treatment and special living conditions in Socium.

Table 1. **Blocking, switching factors, statuses, states**

Norm	Acute damage	Chronics
Absence of inflammation. No "target" in the tissues.	Local acute inflammation, which is gradually fading away, occurrence of a target – source of "need signals".	The damage zone is gradually formed; the inflammation starts and reaches its smoldering level.
Macrophages are in such M1 and M2 ratios which are ready to ensure the inflammation↔restoration dynamics if required.	Macrophages instantly transfer from M2 to M1, and then, some time later, gradually change into M2.	Macrophages pass into the alternative state M1.
SC on duty (mainly hematopoietic ones) are constantly present in the blood flow in the state of readiness / waiting.	The cells of the damage zone release "need signals", thus implementing the readiness state of SC, set to be released from their niches (mainly hematopoietic ones), and the formation of new ones (mainly MSC).	The target cells do not release the "need signal", instead they produce the spectrum of signaling molecules, forming the marker of elimination.
Readiness of progenitors and all the cells, which may transform into MSC, to this transition and the production of MSC, if required.	SC, which were formed and entered the blood flow, recognize the damage zone and move towards it.	The cells of the damage zone and macrophages turns off the readiness state of all the SC producers. There is a double imperception – the damage zone does not release any "need signal", and SC do not see the damage site.
Self-support of the norm state.	Once in the damage zone, SC restore the norm directly and indirectly,via signaling molecules.	The chronics gets established and is in progress.

The specificities of above described states are presented in the comparison table (Table 1).

Considering all the known states of transitory stemness, self-reproduction and specificities of real stem cells [41], it should be taken into account that the chronic is also heterogeneous by the nature of this phenomenon. Importantly, the chronics in the early and older age groups are different. At the early age, the chronics exist as switchable states, whereas in the older age group there is a loss, weakening of functional possibilities, which cannot be switched back to the norm. In natural conditions, aging is also an elimination marker for life and is implemented similarly to the chronics – aging organisms become less adapted in nature due to inevitable accumulation of mutations with age.

The technologies of cell therapy to treat these different types of the chronics should be distinctive. In the present discussion, the analysis is based only on the chronics, characterized with possibility of switching the alternative states. However, the age-related chronics requires a special analysis.

This is the way the chronics are considered from the standpoint of fundamental biology. But historically medicine was formed as something fundamentally special: "Man is not an animal". And everything that relates to a person consciously or subconsciously comes from this. A human positions himself to the rest of the universe. As a result, all laws, mechanisms, principles of the living are automatically ignored, even without allowing discussion. Yes, a human once came from an animal, but it was a long time and it was boundary – an animal and now quite another – Human. Thus arose and confirmed a conceptually inconsistent representation of reality. In reality, however, man is dual in nature. By its psychology, intellect, *etc.*, he is a carrier of Intelligence, and this is his actual principal difference from animals. On the other hand, according to all his biological properties, he does not fundamentally differ from "the smaller brothers" All the differences are not global and correspond to interspecies ones. And the central conclusion from this is that, as a living being, a human is fully realized by the mechanisms of life and obeys the laws of biology. The civilization – "the fruits of the mind" – does not change the mechanisms and laws of biology, but rather block, compensate, or pervert them. This is realized in two ways – by Socium (environmental conditions) which acts "outside" and medicine which acts on what is "inside". Nevertheless, the duality of the nature of human should not be countered, but realized jointly by the conditions of society, and using the mechanisms and laws of biology.

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Хроніка в контексті уявлень фундаментальної біології

В. А. Кордюм

З позицій уявлень загальної біології, аналізується проблема хронічних хвороб («хроніки»). В рамках такого аналізу формується і обгрунтовується уявлення про те, що хроніка є еволюційно вироблений механізм очищення популяції, виду від мутаційного вантажу. Це досягається виключенням систем самовідновлення в організмі, який довго не відновлюється при впливі на нього природних факторів. Відповідно хроніка в природних умовах перетворюється на маркер прискореної елімінації її носія.

Ключові слова: хронічні хвороби, еволюція, самовідновлювальні системи.

Хроника в контексте представлений фундаментальной биологии

В. А. Кордюм

С позиций представлений общей биологии, анализируется проблема хронических болезней («хроники»). В рамках такого анализа формируется и обосновывается представление о том, что хроника представляет собой эволюционно выработанный механизм очистки популяции, вида от мутационного груза. Это достигается выключением систем самовосстановления в организме, который долго не восстанавливается при воздействии на него природных повреждающих факторов. Соответственно хроника в природных условиях превращается в маркер ускоренной элиминации её носителя.

Ключевые слова: хронические болезни, эволюция, самовосстановливающиеся системы.

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