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Free radicals, antioxidants and longevity: aging versus reliability of biological systems

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Motivation and Aim: Aging is a universal process to which all organisms, multi-cellular and unicellular, are subjected. Some researchers consider aging as the last stage of a genetic program of ontogenesis and believe that there are special "genes of aging" which regulate aging and death. Other researchers believe that aging is a stochastic process, the cumulative side result of the pleiotropic action of a large number of regulatory genes, whose useful action manifests itself in the reproductive period and whose harmful influence becomes apparent only after the reproductive period ends. This mini-review is designed to show that the system theory of reliability allows to integrate the programmed events and the stochastic events into the single united theory.
Methods and Algorithms: In engineering, reliability is defined as ability of a device to perform the preset function for the given time under the given conditions [1, 2]. Smilitarily to technical devices, biological constructs are not perfectly reliable in operation, i. e. normal acts of operations alternate with stochastic (random) malfunctions (failures). The field of systems biology, in dealing with the problem of reliability, incorporates investigations of: classification and systematization of failures; mechanisms of failures of biomolecular nanoreactors and mechanisms of realization of the failures in functional breaks; investigations of renewal processes; elaboration of methods for testing reliability and predicting failures. This field was born about 50 years ago. Regular conferences on reliability of biological systems, starting from 1975 in the former USSR, have given the impetus to research in this direction [3]. The special Committee on Reliability of Biological Systems at the Scientific Council on Biological Physics of the USSR Academy of Sciences, to deal with the problems of reliability of biological systems, was organized in 1978, and many prominent biophysicists were the members of this Committee. A quarter of a century after, it has spurred the similar studies behind the former iron curtain under the style of "biological robustness" [4]. Yet, there is the mathematical theory of reliability, not "robustness", and mathematicians consider this theory as a part of probability theory [1, 2]. As said by Immanuel Kant, "in any partial doctrine of nature, one can find as much genuine science as there is mathematics in this doctrine and no more". The problem of reliability has direct bond to the problem of aging of biological systems. The systems reliability approach, which was developed in our papers, is based on several general postulates [5–9]. First, all biological constructs are designed in keeping with the genetic program in order to perform the preset functions. Second, we believe that all constructs operate with the limited reliability, namely, for each and every biological device normal operation acts alternate with accidental malfunctions (recurrent failures). Third, the preventive maintenance, i. e., the timely replacement (prophylaxis) of unreliable functional elements through the

metabolic turnover, that follows the pattern preset in the genome, is the main line of assuring the high systems reliability. Forth, there are a finite number of critical elements of the highest hierarchic level which perform the supervisory functions over the preventive maintenance. And, five, the supervisors also operate with the genetically preset and limited reliability.

Results: On the reliability-engineering basis the universal features of aging, the exponential growth of mortality rate with time (Gompertz law of mortality) and the correlation of longevity with the species-specific resting metabolism (Rubner scaling relation) are explained. The stochastic malfunctions of the mitochondrial electron transport nanoreactors, which produce the anion-radicals of oxygen ("superoxide radicals") as by-products of oxidative phosphorylation, are of first importance. As the reducing agent, this radical affects NAD(P)H/NAD(P)$^+$ ratio, thereby impacting the epigenetic sirtuin regulators of the metabolic repair and renewal processes. As the consequence, the oxidative-stress products and other metabolic slags accumulate with time, resulting the impetus to autophagic or apoptotic cell death with age-associated clinical disorders. Longevity of human brain could reach 250 years should the antioxidant enzyme defence against the free-radical failures be perfect. Furthermore, the systems reliability approach serves as the heuristic methodology for anti-aging pharmacology, in part, in searching the real protection mechanisms of the antioxidant therapy [10]. *In vivo*, the so-called antioxidants, natural and synthetic ones, work not so much as the direct inhibitors of the free radical processes but prevent the formation of the oxygen radicals and free radical oxidation processes in cells and tissues. In terms of the system theory of reliability, antioxidants provide the prophylactic maintenance against reactive oxygen species. For example, synthetic antioxidant BHT (butylated hydroxytolene) prevents generation of the oxygen radicals as by-products of mitochondrial electron transport, while resveratrol and some other flavonoids exert the preventive antioxidant action by inducing the expression of the antioxidant enzymes. At this point, the neuro-hormonal system and regulatory transcriptional and translation factors, along with the organism's microbiota, are of paramount importance.

Conclusions: Thus, from the reliability point of view, aging occurs as the inevitable consequence of the genetically preset deficiency in reliability of the biomolecular constructs while the free-radical redox-timer, located presumably in the special cells of hypothalamus, serves as the effective stochastic mechanism of realization of the genetics program. Furthermore, the systems reliability approach serves as the heuristic methodology for searching the real mechanisms of anti-aging pharmacology, including the antioxidant therapy.

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