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Editorial

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About Drunkard and the Keys which were Not Found

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A drunken person labored long looking for a lost house key under the light of a street lamp. A responding police officer asked the drunk where under the light the key was lost. The drunk replied that he had not lost the key there but it was too dark to search where the key had gone missing..... The current state in molecular genetics and molecular biology in general, involuntarily evoke associations with this anecdote.

For many physicians, biologists, biochemists who are professionally engaged in research in their respective fields, it is clear (even if not always recognized) that the Genome, the Cell and the Organism constitute a very complex and interdependent system. None of the genes work in offline mode independently. Genes modulate (enhance, reduce, compensate) one another's expressions, depending on changes within encompassing systems, including cells, organisms, and the physical, biological and psycho-cultural environmental systems within which the organism is embedded. The study of epigenetics, proteomics, and immunology, among other fields of molecular inquiry, reveals the complex mechanisms whereby genetic expression is mediated by complex, interdependent and fundamentally open biological systems.

A musical metaphor better captures the complexity of the open genome than the mechanistic and atomistic metaphors of bygone centuries. Accordingly, the functioning of the genome can be likened to a holistic, harmonious orchestra performing a beautifully emergent and ceaseless Symphony of Life. The reality is the orchestra, as a functional unit, not the individual violins, French horns and thousands of other musical instruments performing in this metaphor. Discordance is inevitable, but harmonious adaptation is what enables the orchestra to cohere across time. However, the objects of the study of molecular genetics are "separate instruments rather than the Orchestra in its entirety." This reductionist approach promises to explain complicated physiological phenomena in the language and terms of molecular interactions [1], inadvertently echoing the classic mechanism of the XVII century. The replacement of the Cartesian mechanical "gears and wheels" by the various interacting molecules can hardly be considered a fundamental divergence from inadvertent mechanism. Parsimony and practicality have driven atomistic inquiry because approaches to the study of the structure of individual genes and their activity (regulation of their expression) seem relatively simple and clear, while efforts to study the orchestra as a system escape established research protocols and too often defy the scientific imagination. Even if the search is fruitless – under the lantern the drunk stumbles for a lost key.

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The limitations of atomistic thinking were made clear by unexpected small findings from the "Human Genome Project." The project represented a turn to first causes in health and medicine, away from more holistic approach to understanding life and its optimization [2]. But the search for genetic first causes has disappointed as clear relationships between genes and diseases have materialized only in a few well-celebrated instances, such as the case of cystic fibrosis. Disappointing genetic findings on troubling diseases, such as autism and cancer illustrate the limitations of the atomistic paradigm. Moreover, the genomic revolution has failed to deliver promised therapeutic strategies because the relationships between the genotype and phenotype are extraordinarily complex as identical genotypes produce different phenotypes under varying conditions [3]. Indeed, there is a conspicuous lack of progress in the fight against cancer, despite the annual allocation of billions of dollars. Vast amounts of analytical data on the molecular-genetic characteristics of malignant cells accumulated in the past fifty years have not significantly altered the mortality rate from cancer from what it was a half century ago [4].

ED Sverdlov and his colleagues draw attention to the fact that the flawed reductionist approach is graphically illustrated by the low efficiency (in most cases), of targeted therapies for the treatment of various cancers [3]. Disappointing results may have surprised experts in the field of molecular pharmacology, but were quite predictable from the holistic point of view. In all likelihood, the low efficiency of molecular-targeted cancer therapy does not derive specifically from methodical mistakes in the choice of molecular targets, but rather derives from the source paradigm's flawed assumptions about the targeted mechanisms. From the holistic point of view, the strategy of deploying a molecular-targeted therapy for cancer can be likened to an unsuccessful attempt to destroy a holographic image by shattering it into fragments. This strategy is doomed because a holographic image is intrinsically indivisible. From the holistic point of view, a malignancy will be more successfully suppressed by targeting non-specific toxic (systemic) influences, rather than by deploying targeted-based therapy. A more successful approach to treating cancer will no doubt evade us until we more fully acknowledge that cancer is a disease of the whole ORGANISM, and not the genetic apparatus of individual cells [5]. We must consider carefully the words of Alexander Zalmanov, who wrote: "Attempts to find an antidote against cancer infertile because the key is not cancer, not a cancer cell, but patient affected by cancer" [6].

Indeed, it is known that neoplastic transformation of the leaves of many plants (formation of the galls) resulting from the introduction of the oncogene vir-regulon occurs only when the leaf is damaged. The oncogene is introduced (confirmed by PCR), but malignant transformation does not occur until after the leaf is damaged [7]. These observations are supported by data generated by J. Folkman and R. Kalluri, who showed in pathology studies of histological sections of different organs and tissues that separate populations of malignant cells are detected very often. So "dormant" populations of cancer cells in the mammary glands were detected in more than 1/3 of women aged 40-50 years, although breast cancer (as a disease) is diagnosed in no more than 1% of women in this age. In the samples of thyroid glands of people aged 50-70 years, populations of malignant cells

were detected in almost 100% of cases; however, the frequency of the real disease (less than 0.1%) is a thousand-fold lower. The frequent occurrences of histologically-confirmed "dormant" tumor cells (without any clinical signs and signs of growth) were found in the prostate, as well as in other organs [8]. Probably most of us have in the body certain dormant malignant tumors, and cancer itself as a disease only develops in a small portion of individuals. This paradoxical situation is hardly understandable from a molecular genetic standpoint, but is quite compatible with the concepts of the leading role of whole organismic control for tissue differentiation and tumor growth (remember the statement of A. Zalmanov). And so, one of the most effective approaches to cancer treatment may be the deployment of technologies aimed not so much at the direct destruction of tumor cells, but rather at the recovery of the whole organism through supervision (e.g., local tissue control in combination with systemic immune control) over the processes of growth, regeneration, differentiation, planned cell death, etc. [9].

It is important to realize that the main problems of modern medicine are systemic problems occurring at a supramolecular level and therefore cannot be effectively resolved in most cases by the reductionist paradigm's intervention tactics. This argument does not diminish the basic role of the cellular genome, or of the importance of intercellular molecular messengers and membrane receptors, or mitochondrial biophysical mechanisms of cellular energy production. We need to continue to collect analytical information at the molecular level. But it is equally necessary to take the position that the problem of aging or of the prenatal morphogenesis of the embryo and fetus, or regeneration of damaged biological structures, is fundamentally impossible to describe within the framework of molecular interactions. It will be impossible to understand and beat Alzheimer' disease, or infantile autism, or autoimmune diseases, etc., (as well as cancer), without the acquisition of new skills to operate and investigate and comprehend higher levels of organization of living beings. Ultimately, the systemic approach offers greater promise toward optimizing health and well-being.

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