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How nice and easy . . . what a joy it was to believe IN MOLECULAR BIOLOGY!

Any biological system, any organism is an integral whole, not the sum of its parts. Studying these systems requires a comprehensive approach, but today's fashion favors reductionism, which demotes them to molecular components. This approach deters the development of biology and medicine because it often sets false vectors of movement. For example, even if we know down to a detail the genome of an individual, we can never say for sure if this person gets hypertension or diabetes. Breakages of individual genes seldom manifest themselves as a disease—if a gene suffers irreversible damage and does not deliver the required "product," a compensatory increase occurs in the expression of the genes associated with alternative paths of synthesis, and the organism gets, almost always, all the supply it needs. In other words, any complex biological system, the genome including, works as an orchestra, but so far no one knows how to approach the study of this "orchestra"

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"The whole is greater than the sum of its parts."
Aristotle, Metaphysics

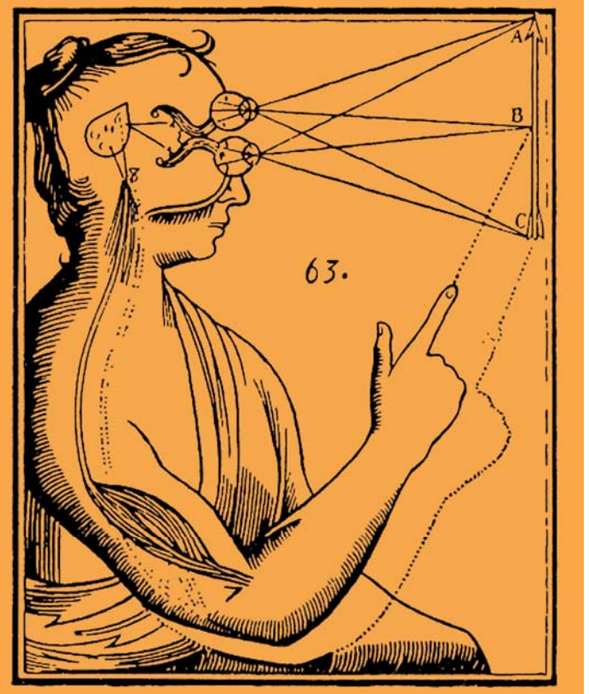
Late at night, a drunk man is searching for his lost keys under a streetlamp. A police officer approaches him and asks where he lost them. In reply, the drunk waves his hand into the darkness: somewhere in the park, but here the light is so much better! This childhood joke comes to mind whenever a conversation turns to molecular biology, "which will soon deal with all our troubles, ailments and other imperfections. And then, we will live for hundreds or even thousands of years! Because old age is a disease that we need to learn how to treat" (from a conversation with a physicist from MIPT). I find that many physicists who take to life sciences soon become very prone to this lyricism. Let us look into this issue for a bit.

About 400 years ago, Rene Descartes, who was admiring a sophisticated tower clock that could play elaborate theatrical performances, conjectured that the functioning of living beings was not intrinsically different from the work of wonderful clocks. This idea seemed logical—if a skillful watchmaker was able to make such an amazing clock, what about another Almighty Creator, with his limitless power of creating and combining "gears" of any shape and size. And he does so to create ants, elephants and all other—flying and jumping, breeding and playing, devouring one another—living beings.

Today, however, we tend to disapprove of the Cartesian mechanism. In so doing, we for some reason overlook that in our attempts to prop the principles and systems that underlie the vital activities of living beings—from the development of fetus to the rational activity of man—against the foundation of intermolecular interactions, we have not gone far from the classical mechanism of the 17th century. All our accomplishments come down to replacing Descartes' mechanical "levers and gears" with molecular ones, which hardly constitutes a crucial difference.

From an interview with Academician Evgeny Ginter (Moscow): "There is a grave disease—ankylosing spondylitis. Almost all the patients have the HLA B 27 antigen. The incidence of the disease is ~1: 1000, and the incidence of the antigen in the population is 1: 20. That is, HLA B 27 will be detected in 50 people out of 1000, but only one of them will develop ankylosing spondylitis. The same applies to all multifactorial diseases"

Key words: living systems, reductionism, holism, autism, malignant growth, microbiome



In the modern era, Rene Descartes became the first consistent advocate of the reductionist worldview to continue the tradition of the ancient philosopher Democritus. *Top*: a drawing from Descartes' *Treatise on Man*, dedicated to the function of the pineal gland. *Public domain*

Reductionism, i.e., the same all-simplifying mechanical philosophy yet clothed in a modern guise, now claims to explain any biological phenomena in molecular terms. Evidence that reductionism is not fit for explaining biological processes in norm and pathology comes, e.g., from the following paradoxes:

• An unexpectedly small practical (medical) outcome from the utterly successful mapping of the human genome, which turned out to be far below the initial expectations.

• The continuing increase in the incidence of cancer and almost the same mortality rate as half a century ago despite the accumulation of huge amounts of analytical data on the molecular genetic characteristics of malignant tumors and the annual billion-dollar investments in fundamental research on this disease and the development of new (not very effective) anticancer drugs (Varmus, 2006).

• The lack of revolutionary breakthroughs in understanding the higher brain functions in norm and pathology against the background of apparent successes of analytical neurobiology.

Why do we have such a situation in biology and medicine?

Let us take the individual genome as an example. It is obvious for most experts, although they prefer not to say it out loud, that the genome works as a Single Whole. No genes ever function autonomously. The genome acquires qualitatively new properties in comparison with the genes integrated into it and relates to them in about the same way as a water molecule does to the hydrogen and oxygen atoms that form it. In both cases, the whole is qualitatively different from the sum of its parts and cannot be predicted from their properties. The latter was called the *emergence* phenomenon.

Being part of the genome, all genes constantly modulate (increase, reduce, or compensate) the activity of their close and distant neighbors, depending on the challenges posed by the ever-changing environment. Metaphorically speaking, the genome can be likened to a remarkably well coordinated orchestra that is playing, without rest or pauses, a wonderful symphony of our life throughout the time stretch allotted to us. It is only the Orchestra that constitutes reality and can be treated as a Single Whole. Individual violins, cellos, horns, and thousands of other musical instruments are only "atoms" in this orchestra, which cannot be withdrawn.

However, genomics (as well as transcriptomics, proteomics, and other "omics") investigates the separate instruments rather than the Orchestra as a whole. The reason is that many researchers seem to know how to study individual genes, but how can one approach the genome as a single system? Well, the light is so much better under the streetlamp.

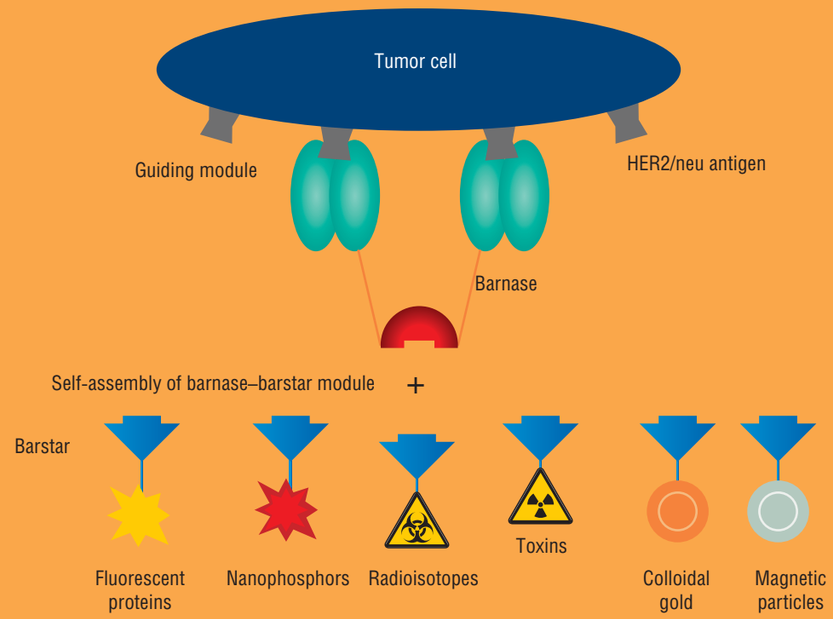
Nevertheless, the discrepancy between the object and the methodology is emerging ever more clearly, despite the powerful opposition of the genetic and pharmacological lobby.

Cancer: treat the patient, not the disease

The deficiency of the reductionist approaches clearly manifests itself in the low effectiveness (in most cases) of *targeted* drugs, which have been used for more than two decades to treat the various oncological diseases (Alekseenko, Pleshkan, Monastyrskaya *et al.*, 2016). However, this low effectiveness of targeted therapy, which came as a surprise to theorists of molecular pharmacology, was quite predictable and understandable from a systemic point of view.

In this case, the failure is due not so much to methodological errors in choosing molecular targets as to the fallacious underlying paradigm. The attempts to defeat cancer with targeted therapy resemble to some extent the inevitably unsuccessful attempts to destroy a holographic image by pinching off its individual fragments while the main feature of a hologram is its fundamental indivisibility. The essentially systemic phenomenon of malignancy is more likely to be sensitive to low-specific general toxic impacts rather than to the targeted "pinches," as confirmed by practice. However, oncologists who use toxic chemotherapeutic drugs have to teeter on the fine line separating the hope of defeating the tumor from the risk of killing the patient's organism.

We will hardly be able to find really effective keys to this problem unless we acknowledge and accept the words said by Abram Zalmanov, a physician, naturopath, and gerontologist, in 1958: "Attempts to find an antidote to cancer are futile because the key is not the cancer itself, not the cancer cell, but the person afflicted with cancer." Unless we proceed from the fact that cancer afflicts the ORGANISM as a whole, not its individual cells (Poletaev, 2010; Poletaev, Pukhalenko, Sviridov *et al.*, 2012).



An example of targeted anticancer drugs with a universal framework module consisting of the barnase protein, a bacterial enzyme, and barstar, its natural inhibitor. These small, highly soluble and stable, proteins can form by simple mixing a surprisingly strong complex through self-assembly. In so doing, the ends of both proteins remain free, allowing for attachment of the various therapeutic agents—from addressing mini-antibodies to most diverse toxins, radioisotopes, etc. There are many uses to this complex.
For example, by attaching the addressing part of the antibody to two barnase molecules and an exotoxin to barstar, we obtained a well-functioning therapeutic construct against HER 2 tumor cells. A crucial advantage of these drugs is their very high specificity.
Adapted from: (Deev, 2017)

Numerous observations illustrate the latter argument. It was shown that the tumor transformation of plant leaves (*gall* formation) under the influence of the introduced *vir*-regulon oncogene does not occur unless the leaves are injured. The oncogene incorporates itself but unless the leaf is further injured (e.g., by a simple puncture), galls do not form (Brencic, Angert, and Winans, 2005). Moreover, transplanted malignant cells cause tumor growth not immediately and, by no means, in all the recipients. It is possible that here too, the induction of tumor growth depends on the severity of tissue injuries when replanting foreign cells (Ruggiero and Bustuoabad, 2006).

Nature has published most exciting data suggesting that isolated groups of nonmultiplying malignant cells are strikingly often found in women and men aged 50 to 70 (Folkman and Kalluri, 2004). It is very likely that most of us carry "dormant" malignant cells in our bodies, but only some of us develop cancer as a disease. This paradoxical situation hardly goes well with the molecular genetic concept of oncogenesis, but is clear and credible from the point of view that places the decisive role with the body-wide censorship control over tumor growth (recall Zalmanov's words).

Data of this kind reinforce the ideas that despite the presence of active oncogenes, under normal conditions tissue-related and body-wide systemic regulatory influences effectively prevent the onset and growth of tumors. It is only when the system control fails that the disease may develop. If so, then one of the most effective approaches to cancer treatment may be the technologies aimed not so much at trying to completely destroy tumor cells by means of external (chemical or physical) factors but rather at restoring the body-wide supervision and control over the processes of cell growth, differentiation, and regeneration as well as planned cell death (Poletaev, 2010).

Autism: healthy mind in a healthy body

Childhood *autism* is another example of a body-wide (systemic) pathology that requires a systemic treatment. The spread of autism is becoming more and more of an epidemic: today the rate of birth of autistic children is one case per every 60 to 80 newborns against one per 5,000 to 10,000 half a century ago.

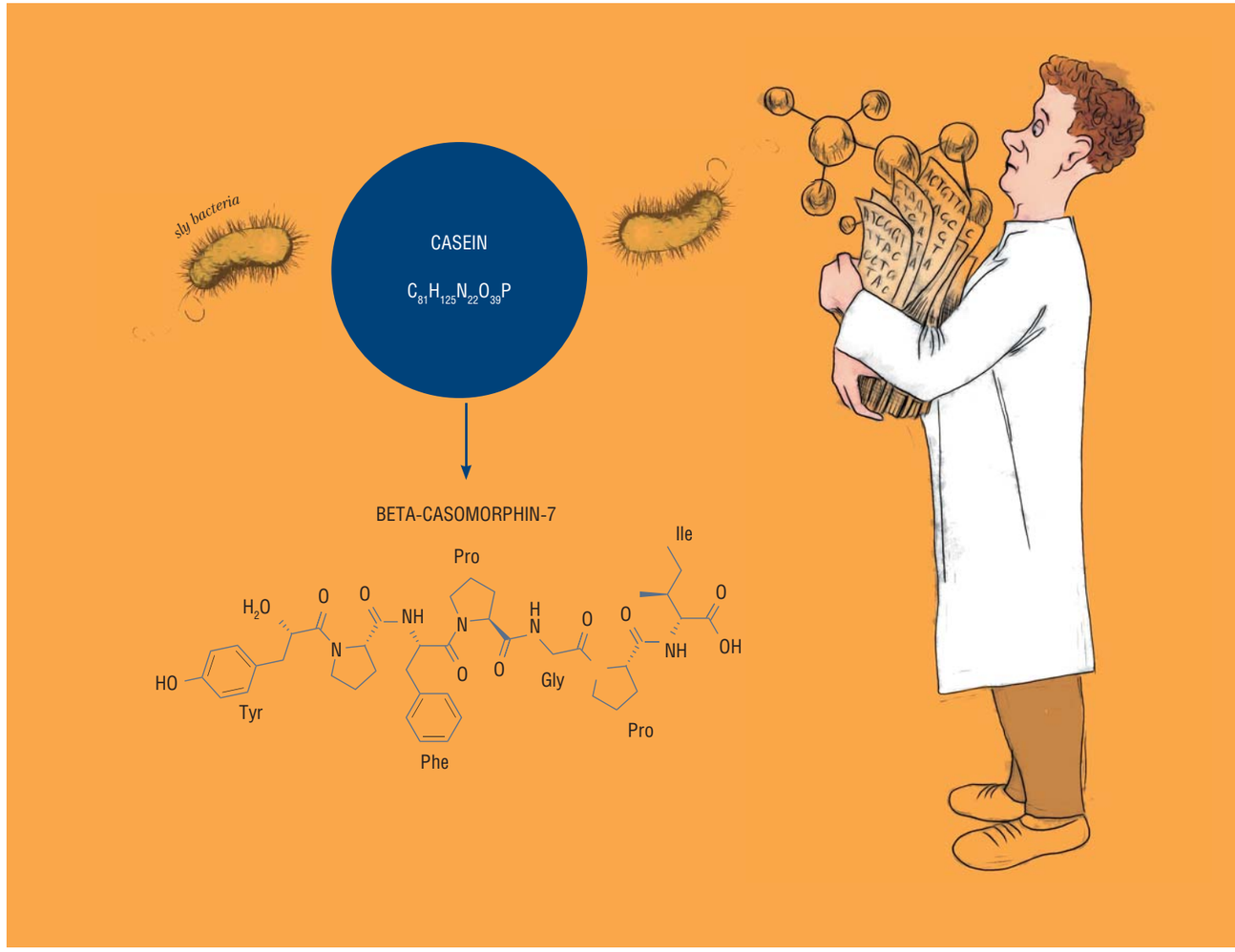
This serves as indirect evidence that in most cases, autism is not associated with genome defects as there are no epidemics of genetic diseases. It is more likely to be due to the aggravating environmental problems (an excess of technogenic pollutants, unbalanced nutrition, microbiocenosis disturbances, microwave radiation, etc.), which cause persistent changes in a woman's body before and during pregnancy (Herbert and Sage, 2013; Poletaev and Shenderov, 2016). The latter include long-term shifts in the production of a number of autoantibodies and cytokines that are adaptive for the mother's body. For the fetus, however, they often become pathogenic and induce many nongenetic congenital diseases, including autism.

Autism is typically characterized by polysystemic disorders, i.e., neurological disorders are almost always accompanied by somatic ones. Not surprisingly, the mortality rate in these children exceeds by a factor of 3 to 10, or even more (depending on the severity of autism), the mortality in healthy children of the same age groups. Note that effective correction of somatic disorders leads to positive changes in the children's behavior, fully consistent with the words of the ancient Roman poet Juvenal: "*Mens sana in corpore sano* (A healthy mind in a healthy body) ". It is not uncommon that individual dietary recommendations coupled with correction of the autistic child's microflora become even more effective for psychoneurological, verbal, and socio–communicative correction than heavy psychotropic drugs. Thus, the views of advocates of the psychosomatic ideology, a semiunderground movement not too long ago, gain new evidence. As well as the ideology of holism as such.

Autism is characterized by changes in the *endogenous opiate system*, which provides emotional reinforcement of one's eating, drinking, and sexual behavior, and these data may show us ways of correcting these children (Poletaev, Poletaeva, and Khmelnitskaya, 2016). One such way could be the use of an opiate receptor antagonist *naltrexon* (Chabane, Leboyer, and Mouren-Simeon, 2000). However, the possibilities of such correction are not limited to pharmacology.

The endogenous opiate system emerged as a system of positive reinforcement of behavioral actions essential for survival of the individual and the species. Opiate receptors are most abundant in the brain and small intestine. The latter may be due to the fact that many foods contain proteins from which *exorphins* are released during digestion. The exorphins are short endorphin-like peptide fragments acting as opiate receptor stimulants. Specifically, the milk protein casein contains several such fragments (*casomorphins*), and the wheat protein gluten contains several *glutorphins*.

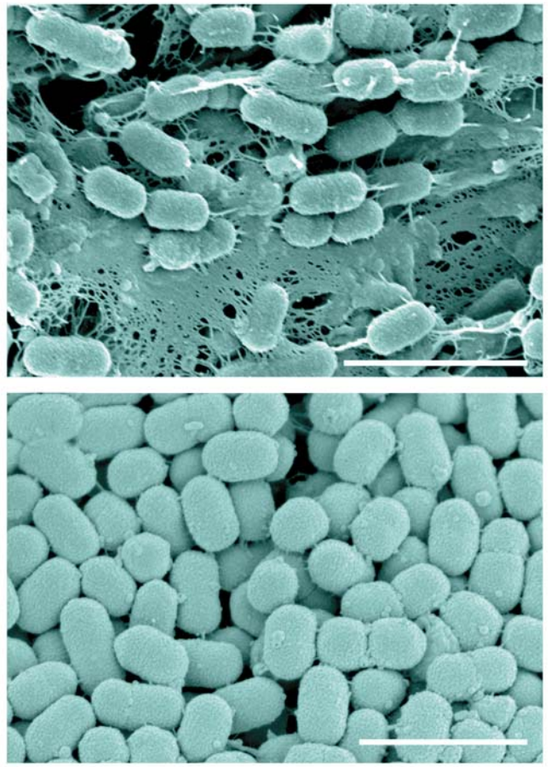
It is believed that eating disorders (bulimia, anorexia) are often associated with an inadequate response of the individual opiate system to food exorphins (Poletaev, Poletaeva, and Khmelnitskaya, 2016). Activation of opiate receptors increases food intake while introduction of their antagonists inhibits this process. These data serve as a basis for the accumulated empirical experience on the positive effects of a gluten- and casein-free diet on the behavior of autistic children, which can be explained by mitigating the excessive activation of their opiate system.



Many foods contain proteins from which, during digestion, exorphins are formed, i.e., short endorphin-like peptide fragments acting as stimulants of opiate receptors. For instance, casein, a milk protein, contains several such fragments (casomorphins, top). It is assumed that eating disorders (bulimia, anorexia) are often associated with an inadequate response of the opiate system to food exorphins

"Let thy food be thy medicine" (Hippocrates)

The exclusion of products that are sources of exorphins is not the only method of health improvement by means of an individually adjusted diet. It is known that more than 80 % of the human immune system is associated with the digestive tube. Small amounts of antigens from food are absorbed from the intestinal villi into the bloodstream in a not fully hydrolyzed form, partially preserving the antigenic properties. Under these conditions, it is very important to ensure immunological tolerance and prevent pathological reactions to food antigens.



Bacteria of the *Prevotella* genus under an electron microscope. These bacteria are among the three microorganisms that determine the human enterotype. One of the strains of these bacteria (*top*) forms special nets, possibly, to stick onto the intestine walls. The other one forms no such nets, which does not prevent these bacteria from flourishing in our intestines

Individual food intolerance—persistent disorders in the immune system, i.e., its abnormal activation and increased production and secretion of proinflammatory cytokines and *autoantibodies* (capable of interacting with the body's own antigens)—may lie at the core of immune–inflammatory diseases such as *Crohn's disease, celiac disease, ulcerative colitis*, etc. (Koshkina, Poletaeva, and Poletaev, 2014). It is the proinflammatory cytokines and neurotropic autoantibodies that may act as the main drivers in the development and persistence of inflammatory changes in the walls of the gastrointestinal tract and behavioral disorders in autistic children. Most of these children demonstrate pronounced food selectivity. This food behavior may reflect a subconscious protective response designed to minimize immune–inflammatory changes in the body by rejecting foods whose antigens pathologically activate certain lymphocyte clones.

From this perspective, it becomes clear why the individual selection of a diet to prevent abnormally high production of biologically active factors of the immune system should not be seen as some kind of shamanism. Instead, this approach can effectively improve the state of somatic and neurological health in autistic children, and in other patients too.

Recall the words by Ludwig Feuerbach (1850): "*Der Mensch ist, was er isst* (Man is what he eats)." Does it make sense to ignore these arguments in the light of all this evidence?

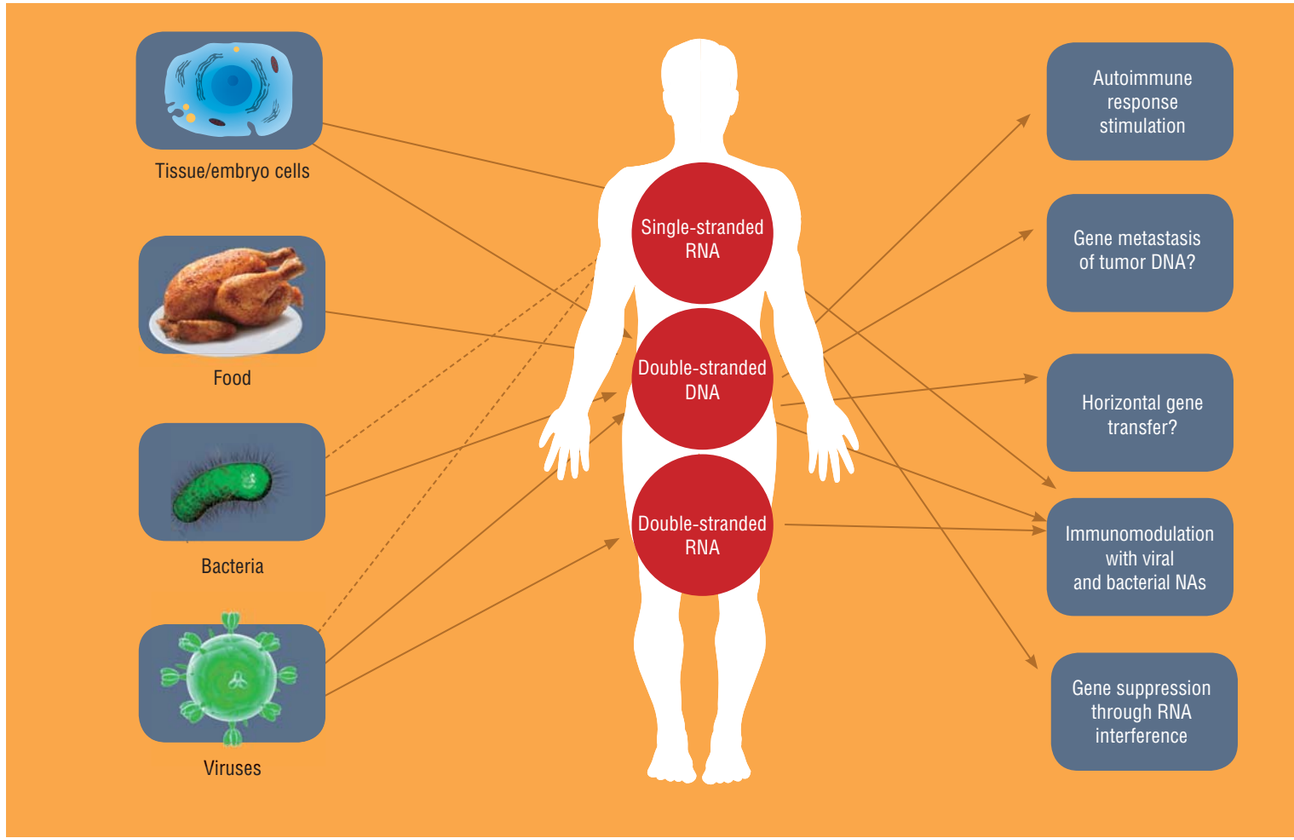
Human microbiota: 100 trillion cohabitants

Every human body is a single quasi-community composed of multitudes of its own cells, bacterial cells, archaeobacteria, fungi, and viruses—a kind of superorganism. Accordingly, the metagenome of this superorganism consists of both the *Homo sapiens*' own genes and those of the numerous microorganisms (*microbiome*) inhabiting its body.

While the human genome contains about 23,000—25,000 genes, the genome of its microbiome contains more than 10 million genes, and science is only beginning to understand its contribution to the activity of our superorganism (Shenderov, 2014). In fact, there is not a single physiological function or behavioral reaction in *Homo sapiens* that would not be related, directly or indirectly, to its numerous microscopic cohabitants.

From the moment a human baby is born, its skin and mucous membranes are seeded with microorganisms, whose quantity and diversity depend on the features of the childbirth, the composition of the mother's microflora, her diet during pregnancy and feeding, the type of feeding, the intake of antibiotics, etc. The body of an adult contains up to 100 trillion bacteria, which are much greater in number than its own cells (Shenderov, Golubev, and Danilov, 2014). The most abundant microflora lives in the large intestine—1.5 to 2 kg of microorganisms in an adult.

Secreting a multitude of neurotransmitters, hormones, growth factors, and other active substances, the intestinal microbiota plays a crucial role in the formation of the central nervous system and in the regulation of its functions. Although the microbiota of each human is relatively stable, nutritional changes and many types of medications (antibiotics, antihistamines, psychotropic drugs, etc.) can significantly affect its composition both inside the digestive tract and beyond,



Nucleic acids are not locked up inside the cells, and many extracellular nucleic acids (DNA and RNA) of both exogenous and endogenous origin circulate through the bloodstream in the human body. Depending on the origin and form of circulation, they cause different biological effects, which manifest themselves at the body-wide level. *Adapted from: (Rykova, Zaporozhchenko, and Laktionov, 2012)*

which in turn inevitably affects the various functions of the macroorganism. Can we ignore all these considerations when we attempt to describe and explain the vital activity of our superorganism?

Blood: all-pervading "ether"

In the times of antiquity, our ancestors perceived blood as a sacred substance, capable, e.g., of rejuvenating the body and stimulating tissue regeneration. Even in Ovid's *Metamorphoses*, the sorceress Medea made Jason's father young again by replacing his blood. Hippocrates recommended that patients drink blood as he believed that blood intake could change the mental and physical properties of man. Pliny and Celsius wrote that sick and elderly Romans drank the blood of dying gladiators, which, they thought, possessed a healing effect.

Blood can be considered as a special substance that functionally conjugates all the organs, tissues, and cells in the body. It is an all-pervading medium, resembling to some extent the ancient concept of *ether*, an all-filling entity that mediates the interactions between all objects in the universe. Blood performs purely economic functions: it delivers oxygen and nutrients and carries away decay products, also serving as a medium for the transfer of colossal arrays of information in the continuous exchange between the numerous structures of the macroorganism and its microbiota. This information is transmitted in the form of control signals of a chemical and possibly physical nature.

The combination of a huge number of hormones, growth factors, cytokines, chemokines, extracellular nucleic acids, antibodies, and other molecules creates a highly ordered information environment, more universal and inclusive

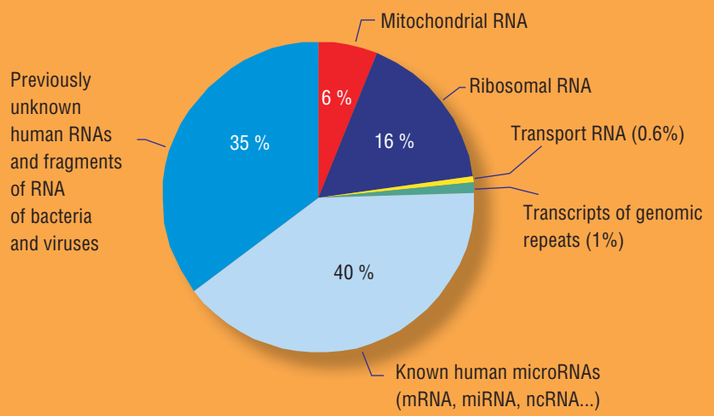
than the information transmitted via nerve impulses, although not as fast in operation. From the practical perspective, it is vital that blood acts as a reflecting, as well as controlling, medium—dynamic changes in the composition of this medium reflect the tiniest changes in the state of individual cells, tissues, organs, and the body as a whole during any interval of time. It reflects both emerging pathological changes, which may lead to future diseases, and existing ones. This "mirror" enables an impartial assessment of the aging patterns of each individual, including their inhibition or acceleration under specific circumstances.

Among intercellular and intersystem communicators, very important are *oligopeptides* (less than 50 amino acid residues), i.e., hormone-like molecules of a protein nature that take part in regulating many physiological functions. These small peptides participate in modulating the neurophysiological mechanisms of basic motivations as well as the learning and memory mechanisms. Changes in the ratios between many dozens of pro- and antiinflammatory cytokines in blood plasma define the vectors of development for local and systemic immune–inflammatory and regenerative processes. However, we have little understanding of their regulatory functions.

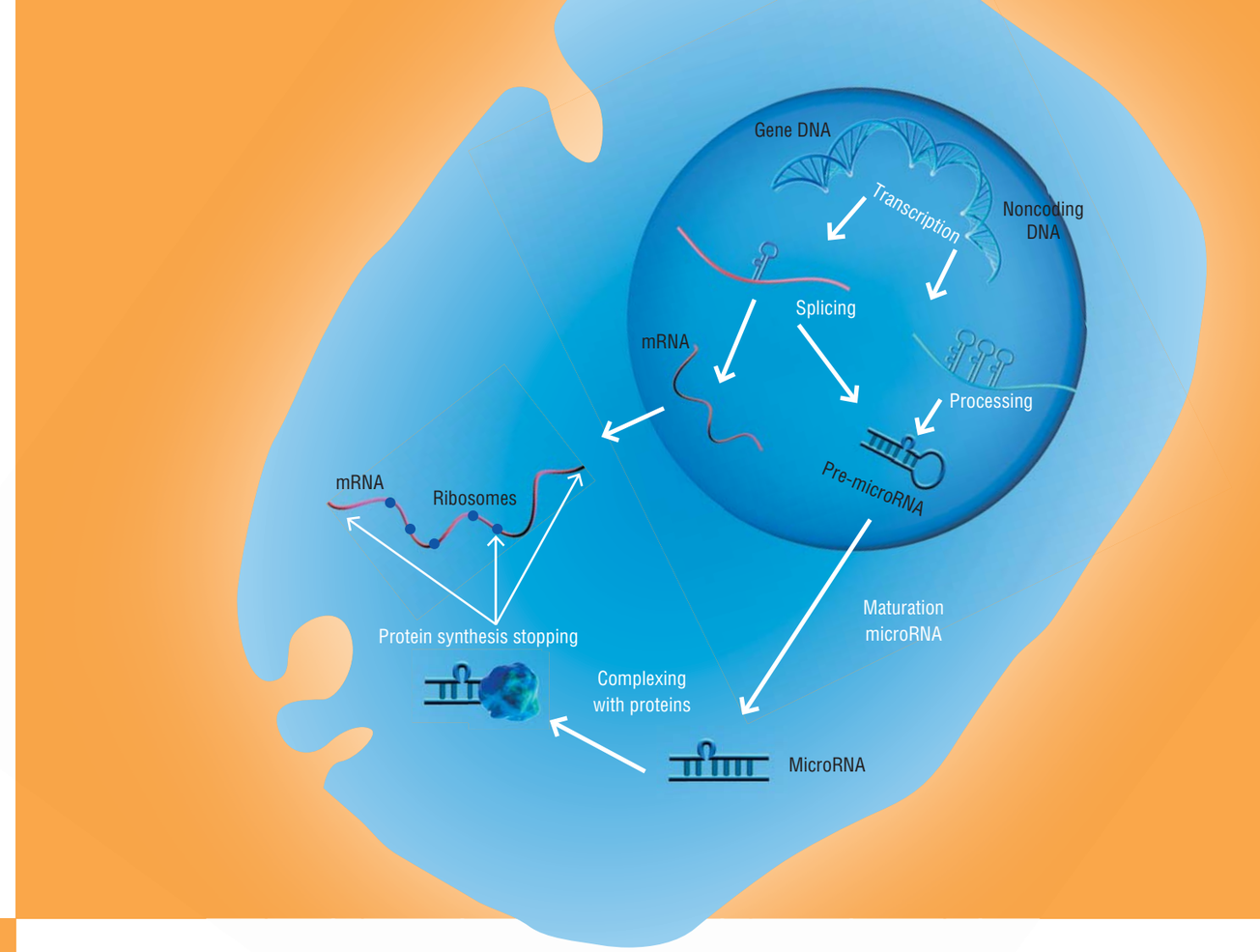
Even less well-understood is the "kingdom" of thousands of short (usually 18—25 nucleotides) *microRNA* molecules that circulate in the blood. Unlike the ordinary messenger RNA, which copies from DNA the information about the structure of a future protein, microRNAs are able to efficiently control gene activity. Thus, they participate in regulating a wide range of physiological processes, but these issues require further study. The regulatory properties of extracellular DNA are even less known to us.

Since the beginning of the 21st century, considerable attention has been devoted to biologically active molecules of extraorganismal origin that participate in regulating the body functions. One such example is the molecules synthesized by symbiotic microflora. It turns out that short-chain fatty acids of microbial origin can attach to certain chemoreceptors of vascular wall cells and participate in regulating the vascular tone. Also, products of partial food hydrolysis that enter the general bloodstream from intestinal villi can affect the emotional status of children and adults (consider, e.g., exorphins).

We are only beginning to understand the role of biologically active microbiota products that enter the general bloodstream like food derivatives. The study of small RNAs, extracellular DNAs, and peptide regulatory plasma molecules is hindered by the high lability of most of them and the high cost of research. Therefore, the most well-understood group may be the most numerous and diverse informational blood macromolecules, i.e., antibodies. They are stable, and their concentrations are 2 to 3 orders of magnitude higher than those of other informational and regulatory molecules. However, this is a topic for another story.



Human blood contains a huge number of hormones, growth factors, extracellular nucleic acids, antibodies, and other molecules, which circulate and combine to create a highly ordered information environment. The little understood blood components include thousands of microRNA molecules, capable of controlling the activity of genes. *Left*: RNA sequences of different origin and with different functions, circulating in human blood; estimated by mass parallel sequencing of blood plasma samples from healthy and sick people. *Adapted from: (Rykova, Zaporozhchenko, and Laktionov, 2012)*

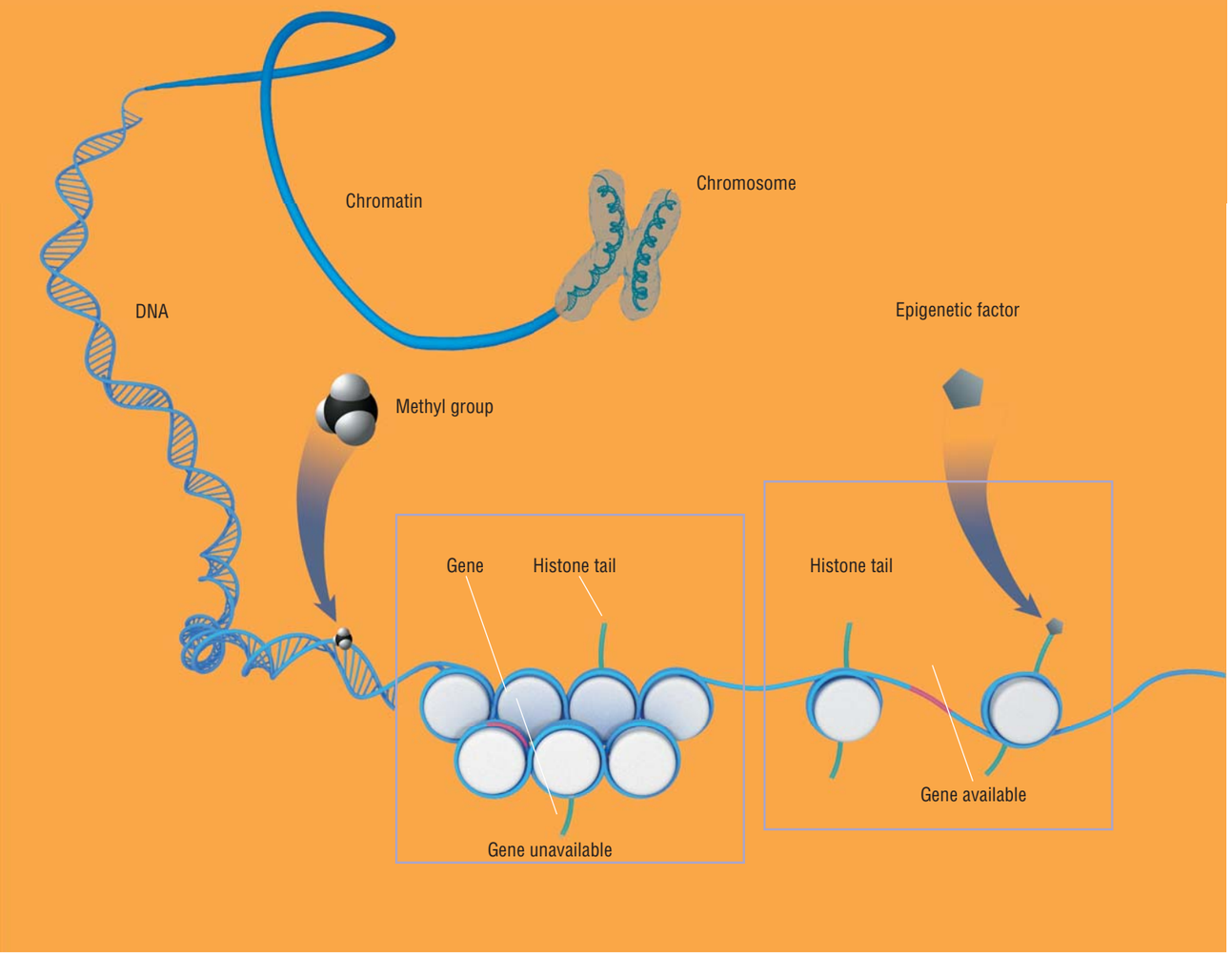


Discovery of the dark genome and a multitude of noncoding RNA, including microRNA, which can directly block protein synthesis, radically changed the views on how genetic information realizes itself, which developed in the second half of the 20th century. *Adapted from: (Vlasov and Vorob'ev, 2012)*

It would be tempting to have at our disposal all the necessary equipment as well as a powerful mathematical apparatus to analyze the correlations between changes in thousands of molecular blood components under different functional conditions. But even if we could analyze everything at once, we should not entertain ourselves with deterministic illusions like those of Laplace, who believed that "an intellect which at a certain moment would know all forces that set nature in motion, and all positions of all items of which nature is composed... for such an intellect nothing would be uncertain and the future just like the past would be present before its eyes..." Alas, living systems are characterized by a high degree of uncertainty, which apparently is an intrinsic feature of any supercomplex system and the main obstacle to studying and working with actual living beings

What to expect and what not to expect from genetic analyses

Genomic programs are the core of all the known biological systems. That is why the genome has powerful defenses. We can only marvel at the utmost ingenuity that created this multifaceted defense of unprecedented reliability. In addition to the most elegant mechanisms for targeted correction of genomic DNA breakages, the reliability system includes repeated duplication of the syntheses of all the essential products in alternative metabolic cycles.



Our DNA contains all the guidelines for building any cell in the human body. However, these guidelines lead to the building of neurons in the brain, hepatocytes in the liver, and some cells transform into cancer cells. Now we know that there are two complementary systems of heredity: the genetic system, which is based on the sequence of nucleotides, and the epigenetic one, which is based on the stable activation and inactivation of genes. One epigenetic way of regulating activity is associated with modifying histone proteins, on which DNA is wound in the cell nucleus. The denser the package, the less accessible the gene is for enzymes that read information from it. Another way is methylation, or adding a methyl group to DNA, which also changes the density of DNA packaging and the availability of genes.
Adapted from: (Zharkov, 2017)

When in need, e.g., the system will produce glucose, essential to all the body cells, not from glycogen but from lactic acid, triglycerides, or amino acids. Thus, if an unlikely unrecoverable gene breakage interferes with the production of a key enzyme and the system can no longer synthesize an important product from the usual substrate, the system will automatically activate other genes that encode the enzymes of alternative synthesis pathways. As a result, the body will still be provided with the necessary product, albeit in a nonoptimal way in terms of energy costs.

We must come to grips with the fact that the genome works as a WHOLE, and by no means should we overestimate the role of individual genes. The gene-centered views, which we have become accustomed to, do not reflect the reality. Recall our metaphor—a symphony performed of a multithousand orchestra. Orchestra! Not individual violins, clarinets, or oboes.

The high reliability of the genome is the main reason why genetic diseases present a rare form of pathology. These diseases arise as "loose ends" left by the Creator or evolution (it is not the terms that matter). The so-called *monogenic diseases*, e.g., phenylketonuria or Rett syndrome, develop in the case of genomic disorders without additional environmental influences, in the same way as gross chromosomal defects, accompanied by simultaneous termination of or interference with the functioning of hundreds of genes (Down's disease, Shereshevsky–Turner syndrome, Patau syndrome, etc.). Molecular genetics has no rivals in prognosticating these diseases.

In the same way as in establishing disputed paternity or ascertaining the degree of kinship, molecular genetic approaches come in useful for studying ethnic perturbations that occurred at different stages in human history, for analyzing the main migrations of peoples, and for clarifying the features of interethnic breeding. In these regard, one cannot overestimate the fundamental importance of molecular genetics methods.

However, when it comes to purely medical purposes and prognoses, these methods are far less helpful. The reason is that fortunately, the combined incidence of genetic and chromosomal diseases in populations is 2—4% or less (Ginter, 2003). Meanwhile, the vast majority of chronic diseases (cardiovascular, oncological, endocrine, etc.) are, in fact, multifactorial diseases, which do not occur unless negative environmental factors appear on the stage. Surely, the likelihood that a given individual will be affected by specific industrial pollutants or microbial pathogens (e.g., leprosy pathogens) is in no way determined by his or her genome. Thus, multifactorial diseases fundamentally defy prediction from individual characteristics of the genome. Hence I reiterate the words by Robert Deth (2014): "...the worship of the myth of genetic diseases does a disservice to those who could be successfully treated, and diverts attention from the real causes of the disease."

To debunk the pseudoscientific "genetic mythology," I think it is important to touch upon the issues of gene polymorphisms, or individual variability of the genome. Random and—in the overwhelming majority of cases—neutral point-like mutations, which occur mainly in noncoding regions of the genome, are the main instrument of evolutionary variability.

The material expression of these mutations is *single nucleotide polymorphism* (SNP), which includes the substitution of one nucleotide for another or the loss of individual nucleotides. Genome-wide screening can help identify many types of SNP that occur more frequently in the genomes of people suffering from certain diseases, e.g., in children with autism. However, the prognostic value of these findings will be low because it seldom happens that random nucleotide polymorphisms can affect the production of enzymes and receptor or transport proteins.

Of course, high SNP may lead to mild metabolic changes, which reduce (as a rule, only slightly) the overall resistance of the body to external influences. This effect will increase the risks of any diseases and disorders, from influenza and myocardial infarction to the birth of an autistic child, but rarely indicates an increased predisposition to a specific pathology. Characteristics of the genome determine, to some extent, the risk of developing atherosclerosis, diabetes, or gastric ulcer, as well as resistance to infections. Thus, during a contact with a leper, 9 out of 10 individuals will be resistant to infection, as determined by characteristics of their genotype. But no one will get the disease in the absence of the causative agent of leprosy.

From this perspective, it makes much sense to rethink and stop taking at face value the largely exaggerated importance of "genetic predictions." Perhaps, a hypothetically accurate analysis of hundreds of thousands of DNA variants (the total individual variability of the genome) based on Big Data approaches might someday be used to assess individual risks. However, in the vast majority of cases, these risks will only slightly (by about 5—15%) exceed the population risks. It is clear that such an individual will likely never suffer from a given disease. The reason is simple – risk is not the same as disease.

Reductionism, practical and ideological

Imagine the following situation: we are looking at canvases painted by great artists, the meaning of which we need to understand and explain. What can we do? We can take a magnifying glass and perform a thorough analysis of the number and width of strokes applied to the canvas by Da Vinci, Levitan, or Picasso; or we can conduct a chemical analysis of the dyes, or an atomic adsorption and spectral analysis of paint samples, etc. The results of these sophisticated and costly studies will be irrefutable. However, they will not let us see the forms and faces; they will not tell us anything about the painted scenes or the artists' ideas. The main truths, their meanings— all that will remain beyond our understanding.

Reductionism is an ambiguous concept. The American microbiologist Carl Wöse suggested that we should distinguish between *empirical* (practical) and *fundamentalist* (ideological) reductionism. The former is essentially a method of analysis, "the dissection of a biological entity or system into its constituent parts in order better to understand it." It does not claim an ability to explain the essence of living things. Fundamentalist reductionism

What a joy it was . . .

we go beyond the scope of intermolecular interactions, we can neither understand nor exhaustively describe the phenomenon of aging, the morphogenesis of the embryo and fetus, the restoration of the structure and function of damaged organs, and many other systemic events.

The main problems of modern biomedicine get stuck on difficulties at the supramolecular level. They cannot be solved in principle within the reductionist paradigm, using electron microscopy or protein electrophoresis. The very fact that the human body is a complex superorganism, a symbiotic community of closely interacting eukaryotic and prokaryotic cells and viruses (and their genomes within a single metagenome), speaks volumes.

It is unlikely that we will understand and defeat Alzheimer's disease or childhood autism or resolve the cancer problem without moving to a fundamentally different methodological paradigm. Completely different from the one we are accustomed to. Innumerable difficulties await us on this path. But someday, we will have to set off on this long and arduous journey.

is a different story—it acts as an ideology that guides one along the path of cognizing and explaining life. Its evident successes in the second half of the 20th century promised, as the fundamentalists believed, to free biology from any specific properties of life not inherent to inanimate matter.

Francis Crick, one of the DNA pioneers, wrote in 1966: "The ultimate aim of the modern movement in biology is in fact to explain all biology in terms of physics and chemistry." The founders of the synthetic theory of evolution (T. Dobzhansky, E. Mayr, and G. G. Simpson), which combines Darwinism with molecular biology, believed that in biology, nothing makes sense outside the scope of this theory, and there are no "fundamental difference between the inanimate and the living world"—the only difference is the degree of complexity.

The "vital force" proposed by vitalists became an object of ridicule. The British physicist John Bernal (1967) wrote: "Life is a partial, continuous, progressive, multiform and conditionally interactive self-realization of the potentialities of atomic electron states." With time, however, it became clear that such features of life as activity, self-learning ability, autoreproduction, etc., including evolution, "cannot be dealt with by promising to reduce these features to simple physical and chemical interactions" (Meyen, 2015). It is needless to prove the importance of analytical information about molecules and cells. However, unless

Crucial changes are emerging in biology and biomedicine. The situation reminds us, to some extent, of the one in physics at the beginning of the 20th century. However, about half a century later, the physicist and philosopher David Bohm (1969) wrote, "...when physics is moving away from mechanism, biology and psychology are moving closer to it. If this trend continues, it may well be that scientists will be regarding living and intelligent beings as mechanical, while they suppose that inanimate matter is too complex and subtle to fit into the limited categories of mechanism."

Unfortunately, no radical changes have occurred yet. So what should we do? How and where should we go to bring closer the revolution in biology that will allow life sciences to enter the new, magical world with an unusual logic?

One of the promising vectors of movement along an unknown path may lie with the study of the evolutionary transition from simple bacteria to complex multicellular organisms. Perhaps, this way we will better understand both the mystery of the emergence of an organism from one fertilized egg and the secrets of intercellular and interstitial cooperation, and many other secrets of living supersystems.

Abandoning the ideas of competition and selection indicates dissatisfaction with hypotheses such as the synthetic theory of evolution: a point-like mutation—selection of those better adapted—dominance in the biosphere. These views are giving way to alternative ideas of symbiotic consortia that lie outside the competitive market and suggest cooperative interactions as a way of formation and evolution of biological systems.

According to these ideas, multicellular organisms emerged as a result of consistent, increasingly complex layers over the existing living forms. In 1967, Lynn Margulis, an American evolutionary biologist, proposed a detailed symbiogenetic theory, according to which eukaryotes arose as a result of successive acts of combining different prokaryotic cells with each other. Her ideas built upon the earlier works of the Russian scientist Konstantin Mereschkowski (1910), who argued that cyanobacteria gave rise to the chloroplasts of green plants, and proteobacteria gave rise to the mitochondria of all eukaryotes. Today, transitions from protozoa colonies to sponges, which have no separate tissues, and from sponges to truly multicellular organisms are sufficiently well-understood. Evidently, as communities of simple organisms were transforming into components of more complex organisms, the former were losing their ability to live autonomously.

In the same way as the reductionism of the 19th-century physics, which demoted all phenomena in the universe to atoms and their components, the 20th-century biology is basically reduced to the molecular biology of genes. However, as the Russian microbiologist Georgy Zavarzin wrote, the organism cannot be viewed as the sum of the genes. "The era of genetic code did not lead to understanding the essence of life because the latter is an emergent property of the system composed of all the interacting components that constitute the organism."

A substance outside the organism has no life. An organism does not emerge from an extract containing all the molecular components in the right proportions. By studying a component, we understand what it consists of and how it works, but we cannot understand how the system (organism) works, of which this component is as an integral part. We can artificially keep these components active for a long period of time, but they cannot reproduce themselves outside the organism.

Deeper down than the level of the cell, biology stops being a life science. It is the context that creates the meaning; it is meaningless to talk about architecture by discussing single bricks (Zavarzin, 2011). Here lies the fallacy of the universal orientation toward the reductionist approach. Someday, we should learn to look at the trees and see the forest and look at the bricks—and see the Kremlin or Chartres Cathedral.

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