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How in the 20th century physicists, chemists and biologists answered the question: what is life?

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Abstract. The most essential achievements in 20th century biology are analyzed and the question of how throughout the last century physicists, chemists and biologists answered the question "What is life?" is considered. The most considerable scientific achievement of 20th century biology, and perhaps of all science, is considered by many to be the discovery by biologist J Watson and physicists F Crick and M Wilkins that resulted in establishing the DNA structure. The related work of well-known scientists of the USA and Europe, E Schrödinger, L Pauling, M Perutz, J Kendrew, and of the Russian scientists N K Koltsov, N W Timofeeff-Ressovsky, G A Gamow, A M Olovnikov, is analyzed. Presently, when the structure of DNA, the process of gene expression and even the genomes of human beings are already known, scientists realize that we still do not know many of the most important things. In our opinion, the 20th century studies of nucleic acids largely ignored the principle of the cyclic organization of DNA. In this connection, we analyze the principle of cyclicity, which in its generality may well complement the concept of the atomic structure of matter.

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From the Editorial Board. We know full well how the boundaries of the science we now call physics have expanded. It becomes especially important in this situation to publish review papers on physics. Alas, difficulties with making a choice arise because the field is too wide. The *UFN* (*Physics – Uspekhi*) Editorial Board arrived at a compromise solution: to print a very narrow range of carefully filtered papers on subjects only indirectly touching on physics but which should prove exceptionally exciting to physicist readers. The review written by V P Reutov and A N Schechter was sent to all members of the Editorial Board and their replies clearly indicated that this paper does belong among those articles that are eminently advisable for printing as exceptions in *UFN*.

V L Ginzburg

Man becomes what he is because of what he does.
Karl Jaspers (1883–1969),
German philosopher

Only to the extent to which man is able to implement meaning which he finds in the outside world, he implements himself.
Viktor Frankl (1905–1997),
Austrian psychologist and philosopher

1. Introduction

Even millennia ago the human mind was deeply interested in the secret of life, in its profound meaning. Nowadays, the literature is virtually bursting with an influx of new facts. The understanding of the physico-chemical basis of biological phenomena is changing rapidly. Nevertheless, even though the deeper understanding of life is now being pursued in many directions and involves practically every science, we still lack a definition of life leading to consensus among scientists [1 – 4]. Furthermore, despite the accumulation of new experimental material, we still lack even an outline of a general definition which, while comprehensive and noncontradictory, would prove valid for all life phenomena. The maximum that we can achieve at the moment is to enumerate and characterize those attributes of living systems that distinguish them from nonliving matter [3 – 6]. It is then natural to ask: (a) what answers were scientists in the 20th century able to offer to the question '*What is life*?', and (b) what prospects has science left to the next, 21st century for answering this question?

Life on Earth exists in a huge diversity of forms manifesting growing complexity of structures and functions. Taken all together, living organisms display numerous attributes. Which of these can be judged the most important? We have no unambiguous answer. Organisms adapt to surrounding conditions in the course of individual development (ontogenesis), while the change of generations acquires evolutionary-historic character (phylogenesis). Organisms have developed the ability to be relatively independent of the environment. One of the more important properties of a living organism is metabolism [4, 5]. Other important attributes of life alongside metabolism are response to external stimuli, growth, reproduction, variation and heredity. Every living organism possesses a dominant ability — the reproduction of its own kind. As classic biologists who worked in this country pointed out: in order to understand a living system, each of its functions should be examined in terms of the history of its formation [1, 6 – 9]. What is one to do, however, if there is no universally accepted point of view among biologists in the issue of the origin of life on Earth?

2. Main hypotheses concerning the origin of life on Earth

Several important hypotheses for the origin of life on the planet Earth have been advanced [7 – 10], as have a number of extended versions [11 – 26]. Listed in chronological order, these basic hypotheses are as follows [7 – 27]:

1) creationism (life was created by a Creator);

2) stationary state hypothesis (life always existed);

3) hypotheses for spontaneous generation (self-generation, or multiple generation of life from nonliving substances);

4) panspermia hypothesis (life was brought to Earth from other planets);

5) biochemical hypotheses (life emerged in the terrestrial environment as a consequence of processes obeying physical and chemical laws, i.e., as a result of biochemical evolution);

6) synthetic theory of evolution consisting of the theories of macro- and microevolution.

The evolutionary approach to the problem of the origin of life is known to be based on the idea of development, which began to form in the 17 to 18th centuries as a methodological principle of cognizing living nature [22, 25]. From the very beginning, the Darwin theory of natural selection helped to classify all species of animals as parts of a common tree of life that comprises animals and plants. After Charles Darwin, the question about the origin of life took on a clear and well-defined form: *how was it that the very first seed of life emerged* [7 – 10, 25 – 27]?

In the 20th century, the hypothesis for the abiogenic origin of life on Earth, developed by J Bernal, A I Oparin, and J Haldane [8 – 10], was the most popular among scientists. According to the panspermia hypothesis proposed in 1865 by German scientist G Richter and given final form in 1895 by the Swedish scientist S Arrhenius, life could have been brought to the Earth from cosmic space [28 – 30].

Among the well-known theories of the origin of life, one popular in the 1970s was the chemical hypothesis for the origin of life, based on self-development of open catalytic systems [17, 21]. No less popular was the 'World of RNA' conjecture which hypothesized a stage in the emergence of life on Earth during which ensembles of RNA molecules carried the functions of both storing genetic information and catalyzing reactions [25 – 27]. At the same time, however, some scientists continued to hold the view that life 'never had a starting point' and is endless; rather, it always existed where conditions were suitable for it (the stationary state hypothesis) [23, 27].

In the 20th century, Charles Darwin's theory of evolution was considerably improved, complemented, and corrected [31 – 34]. Genetics and molecular biology led to new interpretations of evolution, known now as *Neo-Darwinism*, or *general modern evolutionary synthesis* [35]. The elementary unit of evolution in this theory is the *population*, because it is within populations that the hereditary modifications of the gene pool occur. An important role in strengthening the evolutionary synthesis was played by S S Chetverikov's ideas that selection works not through individual traits or animal units but through the genotype of the entire population [36]. *The theory of macroevolution*, as a part of modern evolutionary synthesis, studies the origin of the superspecies taxons (families, orders, classes, etc.), the main directions and patterns in the development of life on Earth, including the emergence of life and the evolutionary descent of humans as a biological species. The second part of the general theory — *the theory of microevolution* — studies irreversible transformations of the genetic and ecological structure of a population, which may result in the formation of a new species [23, 27, 35].

A theory that has attracted special interest in recent decades is the neutral theory of evolution suggested as a hypothesis by M Kimura in 1968 [35]. According to this theory, evolutionary changes at the molecular level are controlled not by Darwin's natural selection but by random fixation of neutral or nearly neutral mutations. Even though such random processes occurred too slowly and imperceptibly, their contribution to the evolution of life on Earth could be very significant. The neutral theory of molecular evolution

states that most of the intraspecies variability at the molecular level, which expresses itself as, for example, protein polymorphism, is neutral [35]. In other words, the neutral theory explains the polymorphism of proteins and DNA as a transient phase in molecular evolution and rejects the interpretation in which most such polymorphic systems play adaptive roles and are maintained within a species by one of the forms of equilibrium-maintaining metabolism [35].

However, none of the above-mentioned hypotheses can be accepted as proven, nor can the theories be regarded as complete and comprehensive [32, 34]. It can be said, therefore, that the questions of the origin of life and the existence of life on Earth are the greatest issues of today's natural sciences, that they have given rise to numerous questions all through the 20th century, and that they have attracted the attention of scientists of practically all disciplines, first and foremost physicists, chemists, and biologists [9, 17, 37 – 40].

3. We have failed to uncover something of *major importance*...

In the middle of the 20th century, one of the most important problems of modern natural science involving the structure of DNA was solved [41 – 43]; this directly involved the biologist James Watson (b. 1928) (see Appendices II – V) and physicists Francis Crick (1916 – 2004) (see Appendix III), Maurice Wilkins (1916 – 2004), and Rosalind Franklin (1920 – 1958) (see Appendix I). However, despite this discovery and intense progress in molecular biology and genetics, we are still unable to explain why DNA is built the way it is and for what purpose. All through the second half of the 20th century it was possible to read in special literature and hear from scientists that in a very short time the human genome will be deciphered, that we will know the structure of all proteins, that the sequential order of all fermentative processes will be sorted out — and that all will be clear. In other words, we shall have solved one of the main enigmas of modern science — that is, we shall understand what life is in terms of physics and chemistry [44]. However, now when we do know what the human genome is, more and more scientists have begun to recognize that we fail to understand something *really major*. There can be no doubt about the importance of new facts. Alas, simple accumulation of experimental data does not add to *understanding*, nor does it yield *a theory*. At a certain stage of cognition, the more important factors are not so much facts as *what* they mean or *what* the more general factor is that the facts point to. Consequently, the most important thing at this stage is to identify the most general and essential aspect which may prove to be *the very major thing* we do not yet understand. This failure to understand is in fact the major obstacle on the way to deeper understanding.

So what is this *major aspect*? Some researchers believe that it is that we do not understand why biological structures are such as they are and why reactions proceeding in cells have the character that they have. We know and understand that for a specific function to be expressed, a very specific structure is required. However, what is one to do if the structure undergoes modification in the course of phylogenesis or ontogenesis, while the function is retained? As a consequence of not understanding such complexities, the gap between knowledge and understanding widens. In Section 16, we shall concentrate in detail on certain of the *major* and the *important aspects* in modern biology and medical sciences that are directly related to physics and chemistry.

4. How to close the gap between knowledge and understanding?

The gap between knowledge and understanding can perhaps be closed, but if not, we can at least try to narrow it somewhat by applying an interdisciplinary approach to studying the phenomenon of life via the close cooperation of physicists, chemists, and biologists. Scientists recognized the need for such an interdisciplinary approach already in the first half of the 20th century. The interaction between different specialists opened new possibilities for analyzing that *absolute*, *generally meaningful*, and *invariant* something that is hidden in every living system [45 – 49]. This, in turn, would help us understand in what manner a system can undergo restructuring, while retaining its internal organization and maintaining normal functions.

Indeed, the recognition of the empirical facts of conservation and the repeatability of certain characteristics of biological objects at different structural and functional levels led to the recognition of the need to study system's stability as one of the fundamental issues in understanding what life is [45 – 50]. The determination of invariant characteristics or relationships within a biological object proved to be one of the most important ways of investigating the integrity of the object [45]. For the first time in biology, an approach to investigation was developed in the second half of the last century which was mostly oriented at studying the stable characteristics of objects. After physics, molecular biology came closest to discovering invariant characteristics that survive despite any changes in organisms. The concept of invariant relation and invariant characteristics became a tool in the structural and functional analysis of biological systems. In this context, invariance in a broad sense is understood as something opposing the unlimited variety and uniqueness of observed natural phenomena, i.e., phenomena stemming from certain repeated unchanged, constant patterns of behavior [45 – 47].

In reality, the problem of the gap between knowledge and understanding does not restricted by these aspects. As science progresses, the number of problems that require the active interaction of all natural scientists — mathematicians, physicists, chemists, and philosophers — will only increase, and the work carried out in the second half of the 20th century provided good evidence of this [1, 14, 37, 39, 40]. One may agree with certain modern models and conclusions drawn from working with these models, or one may argue against them. What does transcend this debate is that the joint efforts of physicists, chemists, and biologists introduce principally new approaches to the process of uncovering the secrets of life, approaches that help in understanding the generality and specific distinctions in the organization of living and nonliving matter [13, 14, 21, 50 – 54]. The deciphering of the structure of DNA is an example of the most successful interaction between physicists, chemists, and biologists attempting to answer the question 'What is life?'.

Now, what were the scientific data which served as the starting point for developing the double-helix model of DNA and for formulating principally new concepts in molecular biology and genetics?

5. The data that served as the basis for the DNA model

Darwin's theory of evolution implied that in different organisms the fundamental mechanisms working in living

systems should be organized in accordance with universal principles [7]. The cell theory formulated in 1839 by the German researchers M Schleiden and T Schwann postulated that all plants and all animals are built of tiny elementary subunits they called cells [55, 56]. An important step on this path was the theory of 'cellular physiology and pathology' developed in 1865 by R Virchow (1821 – 1902). The principal message of Virchow's methodological position was that he was seeking the 'universal biological entity' [57, 58]. Virchow was the first after Schleiden and Schwann to successfully predicate in science the idea that the cell is the elementary form of all living matter. Virchow claimed that the cell was that very universal biological entity and that analyzing complex living organisms in the light of this universal biological entity could lead to developing the theory of cellular physiology and pathology, whose foundation he had built himself [57 – 59]. Virchow pointed time and again to the important role of regulatory systems in the normal functioning of physiological systems: "A sickness is not caused by life in abnormal conditions as such; just the opposite: one falls sick in response to insufficiency of the regulatory machinery" [58]. The concept of the cell as an elementary structure of a living organism was an important step forward in the theoretical interpretation of biology because it was possible and necessary at later stages to seek the basis of heredity only inside the cell [60].

It was very clear at the beginning of the 20th century that cells emerge only from other cells as a result of cellular mitosis [55, 56]. Most cell are capable of growing and then dividing into two daughter cells. The nucleus of the cell also divides in two in the process, and each daughter cell gets a nucleus. The fact that the body of a human or an animal grows to full size from a single cell despite an enormity of the number of cells (about 5×10^{12}) was an indication that the fertilized cell carries all the information provided by the male and female parent individuals. Moreover, this information is quite sufficient for the development and growth of the new organism. The universality of the cellular theory indicated that the mechanisms of inheriting properties and attributes may also be universal [60].

This universality was proved when main Gregor Mendel's heredity laws were discovered [55, 56] and the 'chromosome theory of heredity' was subsequently postulated (1902 – 1903) by W Setton [55, 56, 61]. It is assumed that genetics as a science emerged in 1865 – 1866 when Mendel had formulated his conclusion that 'elements', later given the name 'genes', control how physical properties are inherited [55, 61]. Several years later (1868 – 1869), a Swiss doctor and botanist Johannes Friedrich Miecher-Rüsch (1844 – 1895) discovered in the nucleus of cells a substance which he called 'nucleine' [61]. Later on, this substance was identified as belonging to nucleic acids. We see that while in the 18th century evolutionists assumed the individual — regarded as a set of attributes — to be a unit or element of biological evolution, in the 19th century the cell replaced it as such a unit [55]. Mendel in his papers first suggested a drastically different methodological attitude in which neither the individual nor the cell was regarded as the element of evolutionary heredity, but instead an attribute [55, 56, 61]. In this approach, the integrity of an individual or cell is defined by a set of attributes. Mendel's concept offered a principally new idea of biological integrity. However, the foundation of this idea remained unnoticed, as it needed a completely different theoretical context; this context became available with the advances of genetics which established the concept of the gene as the element of continuous heredity and rejected the concepts of elementarity of the individual and cell [55, 56, 61].

The chemical structure of nucleic acids was the subject of studies by chemists and biochemists in the first decades of the 20th century. The question of '*what are the genes*' was very pressing in the first half of the last century. This question was on the agenda not only of medical researchers, biologists, and chemists: practically all natural scientists attempted to find an answer to it. In 1943, Erwin Schrödinger, one of the founders of quantum mechanics, presented to Trinity College a series of lectures on the theme "What is life?". Schrödinger tried to formulate one of the truly major problems — the problem of the nature of life — and to answer the question of what the gene could be [62]. At that time it was already clear that the secret of life is kept in the chromosomes. "It is these chromosomes ... that contain in some kind of code-script the entire pattern of the individual's future development and of its functioning in the mature state." [62]. According to Schrödinger, the gene is so small that it cannot be anything but a large molecule. The idea that genes exist as macromolecules can be said to be Schrödinger's insight. He assumed, however, that the secret of heredity using molecules lies in quantum theory [62, 63]. Schrödinger's idea on the interconnection of genes and macromolecules inspired Crick and then Watson to solve the problem involved in the structure of DNA.

The British mathematician and cyberneticist Alan Turing (1912 – 1954) came up with interesting conjectures concerning the problems of information coding [64]. In 1935 – 1936, Turing developed a theory which inscribed his name in gold letters in the history of science. This theory — the theory of 'logical computing machines' — is nowadays in all textbooks on logic, the foundations of mathematics, and the theory of computation. The 'Turing machine' is a compulsory element of educational curricula for future mathematicians and specialists in computer sciences. In 1943, Turing was attempting to unravel the secrets of the Lorenz cipher machine used by the German High Command. In the course of this work he first discovered the principle on which any computing system could function. In Turing's opinion, a universal computing machine must be based on permanent and changeable programs [64, 65]. At that moment no one, not even Turing himself, realized that he had come closer than anyone to uncovering the secret of how inherited information is encoded. Indeed, encoded hereditary information is essentially a permanent program and a changeable program, and the metabolism represents a universal machine. There was no doubt that hereditary information and metabolism are linked by a certain code. In the opinion of many researchers, the main secret lay in the mechanism of self-replication [65].

In the mid-1930s, the Swedish chemist E Hammarsten established that the molecular weight of DNA samples extracted from a nucleus under soft conditions exceeded 500,000, which was much greater than the molecular weight of most proteins [55]. This was an indication that nucleic acids as components of DNA may play a role in the realization of hereditary mechanisms no less important than that of proteins and amino acids. However, the first proof of the genetic role of nucleic acids was obtained by the American microbiologist Oswald Avery and his coworkers C MacLeod and M McCarty at the Rockefeller Institute in New York. In 1944, they were able to show that the genetic properties of pneumococci can be changed specifically via high-molecular-weight native DNA [55, 56].

It was thus with the publication of the work done by Avery and his coworkers in 1944 that chemists, physicists, and biologists began to pay attention not only to proteins but to DNA, as well [66]. Until this, the number of researchers who worked with nucleic acids was tiny in comparison with the numerous groups that studied the protein question. In reality, though, some studies of nucleic acids had been undertaken before that [55, 56, 61].

For instance, attempts at deciphering X-ray diffraction patterns of DNA were made in 1938 [55], at the time of the pioneering work of William Astbury on the X-ray structural analysis of proteins. In 1947, Erwin Chargaff established that the four nucleotides in DNA molecules were present in unequal amounts and that the ratio of these amounts varied from species to species. This data showed that the difference between DNA molecules is greater than was allowed by the hypothesis of tetranucleotide structure. The natural consequence was a conjecture that the order in which nucleotides are arranged in the DNA molecule was in some way linked to its specific genetic function [61]. Within the next several years Chargaff showed that the relative content of four bases is not accidental, and in 1950 formulated the famous Chargaff rule stating that the amount of adenine nucleotides is equal to that of thymine nucleotides, and the amount of guanine nucleotides is equal to that of cytosine nucleotides [61]. In fact, the fundamental significance of these ratios could not be properly appreciated until researchers turned to scrutinizing the structure of DNA [55, 56, 61].

6. The profound foresight of James Watson and Francis Crick

As we mentioned in Section 5, Francis Crick was greatly influenced by Schrödinger's book [62]. He was most of all amazed by the problem as formulated by Schrödinger: how to explain space-time events occurring in a live organism from the standpoint of physics and chemistry? At that moment, Crick was studying the molecular structure of proteins under the guidance of Max Perutz and he knew that approximately 20 most important amino acids served as monomer links, or the 'construction blocks' of which all proteins are built. The question he asked was: 'What is the boundary between living and nonliving matter?', and he tried to identify the chemical basis of genetics; he believed that it could be incorporated in high-molecular-weight DNA [67].

Crick's important achievement was that, together with crystallographers W Cochran and V Vand, he developed the mathematical theory of the X-ray diffraction by helical molecules with screw axes of symmetry of arbitrary order, including nonintegral axes [68]. The main implication of their theory was a very special arrangement of X-ray reflections on X-ray diffraction patterns of helical structures. It allowed them to identify the helical configuration of polymer molecules in fibrillar proteins and synthetic polypeptides from the pattern in X-ray photographs. Calculations showed that α-fibrillar proteins consisted of twisted fibers of α-helices. It became clear that the laws of X-ray reflections from structures with screw axes studied in classical crystallography are only a particular case of the general theory developed by Crick and coworkers [68, 69]. There is no doubt that this work inspired attempts to determine the structure of DNA by using structural models. We can say, therefore, that before meeting Watson on his arrival in Cambridge, Crick's interest in the DNA structure remained purely theoretical. At later stages it was Crick who made an important contribution to the analysis of X-ray diffraction patterns of DNA obtained by Wilkins and Franklin.

In 1951, James Watson, at the age of 23, received a grant to conduct research at the Cavendish Laboratory at Cambridge University in the UK, and arrived there in order to study protein molecules in collaboration with British physicists and chemists. What was the reason for Watson concentrating mostly on proteins?

For many years in the 19th and 20th centuries, proteins were believed to be the main molecules inherent in living systems: "*life is a form of existence of bodies built of proteins*" [70]. Many scientists, especially of senior generations, continued to believe that protein molecules possessed some special, not yet understood properties peculiar exclusively to living systems. Some well-known scientists were convinced that genes also have the nature of protein. Even though there was no rigorous proof of that, many researchers arrived by pure logic at the conclusion that genes simply ought to be proteins; besides, the presence of proteins in chromosomes was already an established fact [55, 56, 59].

Nevertheless, despite certain persisting misconceptions, there was an intuitive, subconscious feeling in the very atmosphere of the research process at Cambridge that stimulated scientists to suspect that proteins themselves or nucleic acids and their complexes contained a key to something huge and completely new. It was a conjecture that stemmed from knowing the history of science and from the entire preceding experience of research, a guess that was based not so much on logic as on intuition. Destined to resolve the problem were biologist James Watson and physicist Francis Crick, who yearned to learn what genes are, and if genes consist of DNA, what the structural organization of the DNA molecule is. Watson and Crick understood very well that it is impossible to describe the behavior of an object if it is not known what the object is [67]. However, these two researchers had predecessors who helped them attack one of the most global issues of the 20th century.

7. Maurice Wilkins and Rosalind Franklin

Only one team — that of physicist Maurice Wilkins — studied the *structure* of DNA at the end of the 1940s to the beginning of the 1950s [67]. Initially, Wilkins was part of a larger structure which was organized with the support of the Medical Research Council (MRC) by Sir J Randall at King's College London in 1946.The main purpose of this structure was "*to launch an interdisciplinary attack on the structure of chromosomes and similar structures*" [67, 71]. Wilkins obtained DNA fibers by pulling them out of viscous solutions. He tried to find methods which could identify the complicated chemical structure of the DNA molecule. Wilkins was the first to employ electron microscopy to study the DNA structure. Having placed the cell material under the electron microscope, he saw a "thin or almost invisible DNA filament... being arranged in the form of cobweb fibers" [67, 69]. Wilkins also resorted to interference microscopy, attempting to find a way to measure chromosomes. Later on, he began to study the structure of chromosomal filaments using X-ray diffraction method. The filaments manifested high birefringence which could be an indication of the parallel orientation of long molecules along the extension axis. Together with his student R Gosling, Wilkins recorded an X-ray diffraction pattern of a moistened DNA filament,

which proved to be extremely rich in X-ray reflections: it became clear later that this was a roentgenogram of the A-form of DNA [67]. It is generally believed that the stimulus that prompted Watson to start searching for the DNA structure by X-ray structural techniques [67, 71, 72] was the roentgenogram of the A-form of DNA obtained by Wilkins.

Wilkins, just like Crick, was immensely influenced by Erwin Schrödinger's book [67, 71]. By the time Wilkins began to work at King's College London it had already been learnt that genes dictate how the physical properties of living organisms are inherited. Two publications by American geneticists and microbiologists influenced physicist Wilkins the most. In 1941, the American geneticists George Wells Beadle (1903 – 1989) and Edward Lawrie Tatum (1909 – 1975) formulated the 'one gene–one enzyme' hypothesis according to which the synthesis of each enzyme is determinate by a specific gene [73]. In 1943, as we mentioned in Section 5, the American microbiologist and geneticist Oswald Avery (1877 – 1955), when continuing the work begun by the British geneticist and doctor Frederick Griffith (1879 – 1941), was able to show that the genetic material in chromosomes was DNA, not proteins, as had been assumed before [55, 56, 73]. Avery, who pursued his research at the Rockefeller Institute in New York, demonstrated that inherited attributes can be passed on from one bacterial cell to another via DNA [73]. As for Griffith himself, he became part of the history of science by conducting an experiment which we now know simply as 'Griffith's experiment', in which he established the existence of some 'transforming principle', later identified with DNA [59, 61]. Furthermore, by that time it had already become clear that nucleic acids existed in the chromosomes of every cell. The logical conjecture was that all genes consisted of nucleic acids. Chemists and biochemists determined the nature of nucleic acids and revealed that genes are formed with one of these acids — deoxyribonucleic acid (DNA). It was also proved that genes control the biosynthesis of cell proteins and therefore control biochemical processes in the cell. Despite this, much remained unknown about the structure of DNA itself. It was known at the time that DNA is formed of monosaccharide molecules of the pentose group, a phosphate and four nitrogen bases: adenine, cytosine, guanine, and thymine. However, since the nature of chemical bonds between the nucleotides of which the DNA molecule consists had not been fully understood yet, difficulties in interpreting X-ray structural data arose, and it was not clear how to build a 3D model of DNA [61, 73].

We know that Wilkins and Watson first met in spring 1951 in Naples at a conference on macromolecules [67]. At this conference Wilkins demonstrated an X-ray diffraction pattern of DNA, which had immediate bearing on the 3D model of DNA. Watson says: "... Maurice's X-ray diffraction picture ... was flicked on the screen near the end of his talk. Maurice's dry English form did not permit enthusiasm as he stated that the picture showed much more detail than previous pictures and could, in fact, be considered as arising from a crystalline substance. And when the structure of DNA was known, we might be in a better position to understand how genes work" [67, 74].

At approximately the same time (1951), Rosalind Franklin started working at J Randall's laboratory at King's College London (see Appendix I). This happened because Randall wished to strengthen X-ray structural research of DNA at King's College; Franklin was the ideal candidate for studying DNA structure [67, 69, 71, 72, 75]. Maurice Wilkins became her immediate supervisor. Unfortunately, their relations soured quite quickly since at the beginning Wilkins treated Franklin not as a colleague, but as a technical assistant. Consequently, Franklin ceased to inform Wilkins about the results of her research [67, 75]. She did not feel any need to have her work supervised, which resulted in the *de facto* formation of a second team, led by her, which Gosling joined [67, 69, 71, 72]. Already by the end of 1951 their colleagues at Randall's laboratory were of the opinion that Wilkins prepared the world's best DNA *samples*, while Franklin produced the world's best *X-ray diffraction patterns* of DNA [71, 72, 75]. It is a pity that the literature in this country failed to throw light on the role that Franklin played in the identification of the DNA structure [69, 72]. Between 1951 and 1953 she generated enough material for completing the work on the structure of DNA. Having conducted the X-ray structural study of DNA molecules, Franklin identified the A- and B-forms of DNA. We can now be certain that it was she who obtained the highest-definition X-ray patterns of DNA, which allowed the subsequent conclusion that DNA consists of two helices [69, 72]. At some point, when Wilkins showed Crick one of the X-ray roentgenograms obtained by Franklin, Crick immediately saw the solution: DNA is shaped into a double helix resembling a spiral staircase. On the basis of the results obtained by Franklin, Watson and Crick constructed a model of the 3D structure of the DNA molecule [41, 67].

We should certainly highlight the contribution of the British physicist John Bernal (1901 – 1971) to the crystallographic investigation of macromolecules through the work that he conducted in Cambridge [76 – 78]. Another important achievement was the data obtained by Bernal's student, American chemist and crystallographer, and Nobel Prize Laureate in Chemistry 1954 Linus Pauling (1901 – 1994), who demonstrated that amino acids linked into a polypeptide chain should tend to form helical structures [79, 80]. In 1951, Pauling showed that the helical configuration that he called the α-helix appeared to be a very important element of the protein structure. N S Andreeva, researcher at the V A Engelgardt Institute of Molecular Biology of the RAS, had the lucky chance of working in M Perutz's laboratory at the end of the 1950s to the beginning of the 1960s; she remembers feeling the atmosphere of the creative hunt for truth reigning at the Cavendish Laboratory [69]. In Watson's opinion, "the key to Linus's success was his reliance on the simple laws of structural chemistry. The α-helix had not been found only staring at X-ray pictures; the essential trick, instead, was to ask which atoms like to sit next to each other. In place of pencil and paper, the main working tools were a set of molecular models superficially resembling the toys of pre-school children" [67].

Linus Pauling's results were later confirmed by another Nobel Prize Laureate (1962) Max Perutz (1914 – 2002), who established that synthetic polypeptides built of residues of only one amino acid exist in the form of the α-helix [81 – 84]. The results of X-ray structural studies allowed Pauling to reach the stage of prediction of the type of X-ray diffraction patterns for various helical structures, including that of DNA. Later on, Watson wrote in his book *The Double Helix*: "... Our first principles told us that Pauling could not be the greatest of all chemists without realizing that DNA was the most 'golden' of all molecules. Moreover, there was definite proof. Maurice had received a letter from Linus asking for a copy of the crystalline DNA photographs" [67].

At that time Linus Pauling worked at the California Institute of Technology (USA) and could at any instant switch from studying proteins to studying the structural organization of the DNA molecule. Why was it that it was not Pauling, or Max Perutz, or John Kendrew, but the 23-old completely unknown James Watson, who actively attacked the structure of DNA?

The cause lies in the fact that at that moment W L Bragg, M Perutz, and J Kendrew, whose main field was the study of myoglobin and hemoglobin [85, 86], were at the same time trying to clarify the structure of the backbone of the polypeptide chain which was present in numerous fibrillar proteins and could therefore reflect important principles of organization in protein structures. They were solving this problem by building models — a method described in detail by Watson [67]. Owing to utilizing this method, the first models of the structure of fibrillar proteins and synthetic polypeptides were constructed.

As we mentioned above, the most important achievement was Pauling's data, with which he was able to disclose that amino acids linked into a polypeptide chain should tend to form a helical configuration — the α-helix [87, 88]. Pauling decided to construct the most energy-preferred model of the backbone of the polypeptide chain consisting of planar peptide groups, and then check if it agreed with experimental data. It was later shown that only one structure, the α-helix, exactly corresponded to the criteria formulated by Pauling: it possessed a nonintegral screw axis of symmetry, i.e., had a fractional number of peptide groups per turn (18 in five turns) [69]. At the time classic crystallography rejected such screw axes, because crystallographers assumed then that such axes do not provide dense filling of space. Pauling, however, was seeking the most energy-preferred conformation of the backbone of an isolated polypeptide chain, and assumed that the demands of classical crystallography cannot be applied to fibers [69]. Pauling's model complied with all requirements of stereochemistry and appeared very persuasive [69, 87, 88]. It remained unclear, however, what its X-ray diffraction pattern should be. In the course of the first experimental testing of the α-helix, conducted at Cambridge, Perutz discovered in the X-ray images of α-proteins a reflection confirming Pauling's model [69, 81, 84].

8. James Watson and Francis Crick

We have already mentioned in Section 6 that Watson arrived in London to study the structure of proteins. However, the X-ray diffraction pattern of the A-form of DNA, obtained by Wilkins, inspired Watson to switch to determining the structure of DNA by X-ray structural analysis. This happened in the spring of 1951 in Naples at a conference centering on the structure of macromolecules found in living cells [67]. Watson wrote later that he "proceeded to forget Maurice, but not his DNA photograph. A potential key to the secret of life was impossible to push out of my mind" [67]. Watson was able to get permission to work on the structure of DNA at the famous Cavendish Laboratory already in autumn 1951; the laboratory was headed by the Nobel Prize Laureate (1915) W L Bragg (1890–1971), the founder of X-ray structural analysis. Watson was introduced into the team led by the physicist Perutz, who was working on the structure of hemoglobin, but Watson's immediate supervisor was to be Perutz's co-worker John Kendrew [67]. By that time, Perutz had spent more than 10 years collecting data on X-ray diffraction by hemoglobin crystals and was at last starting to get interesting results [81, 82]. There indeed was a person in Perutz's laboratory who was aware that *DNA was more important than proteins*: that person was Francis Crick, who at that time continued to work on proteins [67]. Again, the question arises: why was it that Bragg and Perutz chose to entrust the X-ray investigation of the structure of DNA to a young biologist who had no idea of what X-ray structural analysis signified?

When Watson came to work at the Cavendish Laboratory, there were problems with modeling the structure of fibrillar α-proteins [67, 69]. In Bragg's words, models of fibrillar α-proteins 'did not wish' to agree with the laws of stereochemistry of peptide type compounds, which had shortly before that been established by Pauling, whose work had allowed him to formulate the famous resonance theorem [79, 80, 89] and to publish persuasive papers on modeling the structure of the backbone of the polypeptide protein chain. On the basis of these studies, L Pauling showed that peptide groups of protein chains consisting of six atoms, $C_\alpha-CO-NH-C_\alpha$, should be flat at all times, while the structure of any compound of a peptide nature must comply with the criterion of fully saturated hydrogen bonds [69].

One polypeptide chain in the α-helix curls into a helix confined by the hydrogen bonds between the groups of the same chain. Pauling was able to construct an energy-preferred model of the backbone of polypeptide chain and showed that only one α-helix in which 3.6 peptide groups (a fractional number!) per turn satisfied all criteria. However, Bragg and Perutz clung to the classical position that such helices do not ensure dense filling of space. The model confirmed later was that of Pauling. However, there was no theory to interpret these experimental data. Help was provided by 35-year-old Crick with his theory of X-ray diffraction by helical molecules with screw symmetry axes of arbitrary order, including nonintegral ones. Crick's theory, developed independently of his two co-authors [68], clearly indicated that α-fibrillar proteins consist of twisted bundles of α-helices, and that the laws of extinction of X-ray reflections from structures with screw axes used in classical crystallography are only a particular case of Crick's general theory [69].

By the time the work of studying the structure of DNA was launched, Crick thus had had his own theory of diffraction of X-rays by helical molecules with screw symmetry axes of arbitrary order, while Watson had a passionate urge to investigate the intricate structure of DNA. Working on a problem which they formulated as the problem of the borderline between the living and nonliving matter, Watson and Crick attempted to find a chemical foundation of genetics which, as they assumed, could be hidden in the structure of DNA. Pauling's success achieved with the polypeptide chain gave Crick the idea that similar success might be achieved with DNA as well if they followed Pauling's path. We ought to point out here, nevertheless, that it was impossible to simply copy the experience of working with protein α-helices to the study of DNA helices. New approaches were required, and at that moment Crick and Watson had not even suspected it [69].

Strictly speaking, however, Crick and Watson had no accurate information of whether DNA contained helical segments. When they started, they only possessed X-ray structural data obtained by W Astbury in the 1940s [55, 59, 67]. These data testified that DNA is characterized by a certain stable and somehow ordered structure. At the same

time, Crick and Watson nurtured a guess and hope that perhaps DNA also has the helical structure found in proteins. Both the guess and the hope stemmed from their opinion that the helical structure led to more dense packing of biological material than any other [67].

Crick and Watson were seeking a solution to the question of the structure of DNA all through 1952. At the same time, in the USA Pauling was working on the spatial structure of DNA [69, 90, 91]. Watson and Crick were fully aware that one might start from very different combinations of facts and nevertheless ultimately arrive at identical results. Hence, they knew that their work has to be done rapidly. In 1952, Pauling suggested a three-chain model of DNA with sugar–phosphate backbone at the center [90, 91]. Five scientists thus reached the final lap to a great discovery of the 20th century: biologist Watson, chemist Pauling, and three physicists — Crick, Wilkins, and Franklin [67, 69, 71, 72, 90, 91].

Having built a double helix of wire, a construction higher than a human, Watson and Crick tried to build into it the nitrogen bases attached to one another by hydrogen bonds. They hit upon the correct structure of DNA when they changed from nitrogen bases in the enol form ($R_1R_2 - C = C - OH$) to bases in the ketone form ($R_1R_2 - C = O$). Once Watson and Crick started to think about the ketone form of nucleic bases, it became perfectly clear how DNA bases can produce complementary pairs by forming hydrogen bonds between them [67].

Using the rule of equal purine and pyrimidine bases content of DNA (the Chargaff rule), as well as the data of X-ray structural analysis obtained by Wilkins and Franklin, Watson and Crick assumed that the DNA molecule formed a double helix (not the triple helix suggested by Pauling) and consisted of two complementary chains. The two-chain model was favored by the well-known fact that all important biological objects always form pairs. To come up with this hypothesis it was necessary to find such a configuration of DNA which would be most favorable stereochemically and at the same time would not contradict Chargaff's rule and the X-ray structural data obtained by Wilkins and Franklin [67].

9. Is the knowledge of the DNA structure sufficient to answering the question 'What is life'?

"We have just uncovered the secret of life!" These are the words by which Francis Crick announced the discovery of the structure of DNA on 28 February 1953. James Watson was always more reserved in showing his emotions. The DNA double helix composed of two chains of deoxyribose phosphate joined by pairs of bases played an enormous role in learning the molecular foundations of life. It became clear that hydrogen bonds connect adenine to thymine and guanine to cytosine. In view of this, Watson and Crick postulated the following model of DNA [41, 67]:

(1) Two strands in the structure of DNA run around one another and form a right-twisted helix.

(2) Each strand is composed of repeated residues of phosphoric acid and deoxyribose sugar. Attached to sugar residues are nitrogen bases (one to each sugar residue).

(3) The strands are fixed relative to one another by hydrogen bonds which connect nitrogen bases pairwise. As a result, the phosphate and carbohydrate residues sit on the outer side of the helix, and the bases are inside. The bases are perpendicular to the axis of the strands.

(4) There is a selection rule for forming pairs of bases. The purine base can attach to the pyrimidine base; furthermore, thymine can attach only to adenine, and guanine only to cytosine.

(5) It is possible to swap: a) bases in a given pair; b) any two pairs of bases — this will not disrupt the structure but will drastically change the biological activity of the molecule.

The main physical parameters of DNA are as follows: the diameter of the double helix — 2 nm, the distance between neighboring pairs of bases — 0.34 nm, one twist of the helix contains 10 pairs of bases. The length of all DNA molecules in all chromosomes of a single human cell is about 2 m. Since a human body comprises approximately $5 \times 10^{13} - 10^{14}$ cells, the total length of all DNA molecules in a body amounts to 10^{11} km, which is a thousand times greater than the distance from the Earth to the Sun [44, 55, 56, 59].

The principles of packing DNA into chromosomes were subsequently clarified. To pack a strand of DNA about 2 m long into a nucleus about 1 μm in diameter, DNA is wound around a complex of nucleic proteins, known as histones. As a rule, the DNA strand makes about two turns about each complex of histones. This produces a structure called nucleosome. It looks like beads on a string. One nucleosome is the site of about 200 to 250 pairs of DNA nucleotides. Fragments of DNA (50 to 60 pairs of bases) called linkers remain in-between nucleosomes; they function as connecting chains. This is the so-called first level of compactization. At the second level, structures are again twisted into a helix. What has been compacted at the first and second levels of compactization again undergoes compactization — loop-like or helical — at the third level [44, 55, 56, 59]. Helical packing is thus the main principle of shortening the length of DNA strands, at the same time increasing their strength and protecting them from damage.

Once the structure and the main physical parameters of DNA became known, the gene ceased to be a mysterious entity, now given the status of a real macromolecular object. It also came to be known later that one of the DNA strands serves as a matrix on which the other is created. Two strands of the DNA molecule separate at points of hydrogen bonds; the process much resembles unzipping a zipper. A new DNA molecule is synthesized on each half of the older molecule. Copying (replication) of DNA proceeds by way of building a complementary copy on each existing strand of DNA as on a matrix. In this way, one double-helical DNA molecule yields two absolutely identical double helices — precisely what is needed for passing on the genetic information when the parent cell divides into two daughter cells. The stage-by-stage materialization of genetic information is also based on the matrix principle: another information molecule, RNA, forms a complementary strand on one of the strands of DNA, and in turn serves as a matrix for synthesizing proteins on whose quantity and quality the structure and function of a specific organism depend. The sequence of bases thus functions as a matrix or template for constructing new DNA molecules [44, 55, 56].

How significant is this discovery for uncovering the secret of life? We know that in science a researcher turns to philosophy when under the pressure of conceptual difficulties in its particular field of science (Albert Einstein). On the one hand, knowing the structure of DNA is not sufficient in itself for answering the question "What is life?". On the other hand, it was this discovery which made it possible to move much closer to understanding that *absolute, generally mean-*

ingful, and invariant something which is built into every living system. It was this discovery which lifted one ages-old philosophical question about the *interrelation of the potential and the actual* (*or the manifested*) to the rank of scientific problems. It was this discovery which led to linking the *information* on the structure and properties of an organism to *organisms themselves, their structures and properties*. Finally, this discovery not only generated numerous questions but also handed over a key to answering them. This key is the matrix principle, or principle of complementarity. Thus was solved the fundamental problem of replication of genes, which had remained a puzzle for all geneticists for so long. And while this fundamental problem was being solved, experimental proof was obtained for the matrix principle of reproduction of hereditary material, which had been predicted already in 1927 by the great Russian geneticist N K Koltsov [92 – 94].

10. N K Koltsov's idea of the matrix replication of biological molecules

In 1927, at the Third All-Union Congress of Zoologists, Anatomists, and Histologists, Nikolai Konstantinovich Koltsov (1872 – 1940) presented his talk, ''Physico-chemical foundations of morphology'', in which he expanded the all-biology principles *omne vivum ex ovo* (every life from an egg) and *omnis cellula ex cellula* (every cell from a cell) by declaring the principle *omnis molecula ex molecula* — every molecule from a molecule [92 – 95]. What he meant was 'molecules of heredity', and his pioneering idea was that the reproduction of these molecules is the foundation of the morphophysiological continuity in the organization of living organisms. N K Koltsov imagined these molecules of heredity as gigantic protein macromolecules forming the axial genetically active structure of chromosomes or, in Koltsov's terminology, the 'genoneme' [92 – 95]. The genetic information was thought of as encoded not in the sequence of DNA nucleotides but in a sequence of amino acids in the high-polymer protein strand. N K Koltsov connected the transcription process with the replication of the protein component of the nucleoprotein basis of the chromosome. Therefore, the essential core of the matrix principle formulated by Koltsov postulated that nature first prepares a sort of cast or negative image of the information carrier and then produces an exact copy of the original carrier from this negative. Although, instead of proteins (as Koltsov hypothesized), DNA proved to be the hereditary molecule, this idea did stimulate thinking about the structure of hereditary molecules and the mechanisms of their reproduction. The experimental verification of the matrix principle of doubling the DNA molecule was found, thanks to Watson and Crick, 26 years later. At the moment, the matrix principle of replication of information described by N K Koltsov is used for analyzing many types of information systems. In the opinion of S E Shnoll, the idea of matrix replication of biological macromolecules, or the matrix principle of transmitting hereditary information, is ''the central idea of the 20th century in biology, equal in its importance to the ideas of quantum mechanics'' [95].

L A Blumenfeld and S E Shnoll suggested time and again that for physicists the idea of matrix synthesis was especially easy to digest [40, 95]. Without this idea it would be nigh impossible to imagine how monomers in a polypeptide strand could form the right sequence under ordinary chemical reactions. Nor would it be possible to identify this correct sequence by applying specific enzyme catalysts, because the required degree of selectivity cannot be achieved under such conditions. The frequency of errors in polymer structures would be very high — something physicists understood very well [95].

11. N W Timofeeff-Ressovsky's conclusion: a gene is a tiny compact structure

Outside the USSR, N K Koltsov's idea of matrix replication of biological molecules was developed by Nikolai Wladimirovich Timofeeff-Ressovsky (1900 – 1981). In 1935, the Russian biologist and two German physicists, K G Zimmer and M Born's student M Delbrük, published their famous paper [96]. In this paper they measured the frequency of mutations in *Drosophila* fruit flies as a function of intensity of radioactive irradiation and arrived at two important conclusions:

(1) A jumpwise change in a gene caused by ionizing radiation has a quantum nature, begins with the generation of nonequilibrium energized states of the gene, and results fairly infrequently in inherited changes (mutations) in the atomic structure of the gene.

(2) A gene is a small compact structure consisting of approximately 10^3 atoms.

Therefore, assuming that mutations are caused by a destructive quantum hitting the target (gene), they were able to evaluate the size of this target. The gene proved to be of a molecular size [40, 95, 96]. Schrödinger's idea that a gene is so small that it cannot be anything but a large molecule (macromolecule) [63] is closely related to the paper by N W Timofeeff-Ressovsky and his co-authors [96]. In the opinion of L A Blumenfeld, the importance of this work for biology can be compared with the importance for physics of Rutherford's famous experiments on bombarding a thin metal film with alpha particles, which led to the 'planetary' model of the atom [40].

The paper reporting experimental results of Timofeeff-Ressovsky and his colleagues [96] was written in such a way that the exposition of the results obtained was accompanied by a profound theoretical analysis. This paper [96] pushed the idea of a gene as macromolecule and of the matrix properties of molecules still deeper into the minds of physicists [40, 95]. When Schrödinger presented his famous lectures at Dublin University, he derived his approach from the work of Timofeeff-Ressovsky and colleagues and N K Koltsov's matrix concept, assuming that this outlook and these concepts were generally accepted by biologists [95]. Schrödinger's book, in turn, later stimulated a constant inflow of professional physicists to biology, the future Nobel Prize Laureates Crick and Wilkins among them. When Schrödinger's lectures were published as a book [63], J B Haldane responded to it with an article in *Nature*, stating that the concept on which Schrödinger had based his analysis was not generally accepted in biology, but belongs to a Russian biologist [97]. The next fundamental step was the discovery of the DNA double helix by the biologist Watson and the physicist Crick.

12. "Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid" — a paper published in *Nature*

Watson and Crick described their model for the first time in the paper ''Molecular Structure of Nucleic Acids: A

Structure for Deoxyribose Nucleic Acid'' in the April 1953 issue of *Nature* [41]. Before putting it in the post, Watson and Crick showed it to Wilkins, Franklin, and Gosling, who on the same date sent their own papers with a description of their respective contributions to the solution to the problem [42, 43]. Sometimes these events are not written up quite correctly, creating the impression that Watson and Crick posted their paper without first discussing it with their colleagues Wilkins and Franklin [69]. In view of this, we would like to draw the readers' attention to a phrase in the paper by Watson and Crick [41, p. 737]: ''We have also been stimulated by knowledge of the general nature of the unpublished experimental results and ideas of Dr. M H F Wilkins, Dr. R E Franklin and their co-workers.'' The paper by R Franklin and R Gosling also contained their acknowledgments: ''We are grateful for ... Drs. F H C Crick ... for discussion.'' And slightly preceding it: ''Thus our general ideas are not inconsistent with the model proposed by Watson and Crick in the preceding communication.''

To summarize, three smallish papers, each about two pages in length, were published on 25 April 1953 in *Nature*: the model of Watson and Crick [41], the data of Wilkins's team [42], and the data of Franklin and her assistant Gosling [43]. On 30 May 1953, Watson and Crick published a paper on the role of the DNA structure in the replication of genetic information [98], and on 30 July of the same year Franklin and Gosling published the proof of the double-helicity of DNA [99]. These publications built the foundations of molecular biology and are regarded as one of the main achievements of science in the 20th century.

In their paper ''Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid'', Watson and Crick stated: ''It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material'' [41]. When the mechanism of semiconservative replication was confirmed experimentally, it became clear to most biologists that the sequence of bases in the nucleic acid somehow determines the sequence of amino acid residues in the structure of the protein, as well. However, it was not a biologist, but a physicist, Georgii Antonovich Gamow, who formulated the idea of the presence of genetic code [100].

13. G A Gamow's idea of a universal code

It must be said that physics as an interdisciplinary science has played an enormous role in solving many fundamental problems in biology, and in molecular biology in particular. A characteristic tendency for many physicists was not just to seek the correct solution to the problem but also to try and make the proof laconic, complete, and logically impeccable. John Bernal reckoned that spotting a problem is much more difficult than finding its solution, because the former requires imagination, while the latter only know-how. In 1954, a physicist of Ukrainian–Russian origin (born in Odessa, then attended school and worked in Petrograd/Leningrad), Georgii Antonovich Gamow (1904 – 1968), formulated a specific question for deciphering the genetic code and published a paper on the triplet structure of the information code of the DNA molecule [100 – 102]. What were the initial premises for this conclusion?

Gamow started with the most general assumptions. He knew that all living organisms are based on proteins whose synthesis is controlled by nucleic acids. The method of encoding information using the four-letter alphabet of nucleotides is universal. Each word in the genetic text is the name of the amino acid, and each sentence defines a protein. We know that proteins consist of 20 amino acids. If the alphabet of life has four letters, how are the words constructed of them? G A Gamow formulated exactly this question in 1954. Obviously, the number of words should be at least 20. If we assume that each word consists of two letters, it gives us just $4^2 = 16$ different pairs. This is not enough. Gamow assumed that each word most likely consisted of three letters. Crick's new experiments and the work of American biochemists M Nierenberg, S Ochoa, H Khorana, and C Anfinsen showed that G A Gamow's idea of universal code was correct [55, 56, 59,103]. The DNA model of Watson and Crick and then G A Gamow's idea of universal code predetermined our understanding of the molecular foundations of life on Earth. Watson wrote about G A Gamow's important contribution to the process of learning the molecular essence of life in his book *Genes, Girls, and Gamow: After the Double Helix* (2002) [101].

14. Nobel Prize in Physiology or Medicine 1962

Before 1953, the leader among natural sciences was physics, with its *relativity theory* and *quantum mechanics*, but biology made a decisive move to the front with the discovery of the principles of the organization of DNA. The double helix launched the era of molecular biology in modern biology, since the structure of DNA gave the key to the mechanism of exact duplication of genetic material [98]. In 1962, biologist Watson and physicists Crick and Wilkins received the Nobel Prize for Physiology and Medicine ''for their discoveries concerning the molecular structure of nucleic acids and its significance for information transfer in living material'' (see Appendices I – V). Watson at that time was 34 years old, and Crick and Wilkins were 46. In his presentation speech introducing the laureates of the Nobel Prize, Professor A Engstrom, member of the Staff of Professors of the Royal Caroline Institute in Stockholm, emphasized that ''The discovery of the three-dimensional molecular structure of deoxyribonucleic acid — DNA — is of great importance because it outlines the possibilities for an understanding in its finest details of the molecular configuration, which dictates the general and individual properties of living matter.''

It is generally accepted that molecular biology was indeed born with the discovery of the structure of DNA. In the process, DNA earned the title of the 'principal molecule of life' and the basis of all living matter. In A S Spirin's metaphorical expression, proteins, which in the past were treated as the main component of living systems (''life is the mode of existence of bodies built of protein''), were 'dismissed' from all administrative posts and 'appointed' to junior positions of catalysts serving the life cycles of DNA [26]. The role of nucleic acids of the other type — RNA — reduced to that of intermediaries created on DNA matrices and controlling the synthesis of proteins. The DNA $\rightarrow$ RNA $\rightarrow$ protein diagram, in which arrows stand for irreversible processes of transcription of information, became very popular [26]. It is now known as the ''central dogma of molecular biology'' [26].

15. A M Olovnikov's idea of the role of telomeres in cell mitosis and the Nobel Prize in Physiology or Medicine 2009

The number of hypotheses for the nature of ageing is quite substantial, running to several dozen. We shall mention only one of them, taking into account the role of the genetic machinery in ageing. In 1971, the Russian scientist Aleksei Matveevich Olovnikov assumed that in each replication in somatic cells certain features of the functioning of replication enzymes (DNA-polymerase) cause underreplication of the end segments (telomeres) of chromosomes [104]. As a result of the repetitive shortening of chromosomes in each mitosis, under-replication involves those regions of the genome which are important for the survival of cells and leads to their death and to the ageing of organisms [104, 105].

In 1985, American scientists Carol Greider and Elizabeth Blackburn discovered the enzyme telomerase in cells [106] and in 1998 they succeeded in 'rejuvenating' a cell culture using this enzyme [107]. Later on, these researchers, independently of A M Olovnikov, came to a similar conclusion: the shortening of chromosomes in each mitosis causes the ageing of cells [107]. Jack Szostak was the first in the world to succeed in constructing a yeast chromosome. Furthermore, J Szostak's work helped in understanding the mechanism of recombination of chromosomes [108]. This research was rewarded on 5 October 2009 by the Nobel Prize in Physiology or Medicine.

Three American researchers thus received the highest scientific distinction in 2009: Elizabeth Blackburn (University of California, San Francisco, CA, USA, born in 1948 in Australia), Carol W Greider (Johns Hopkins University School of Medicine, Baltimore, MD, USA, born in 1961 in California), and Jack W Szostak (Harvard Medical School, Boston, MA, USA, born in 1952 in London). The press release of the Nobel Committee for Physiology or Medicine stated that the three scientists "have solved a major problem in biology: how chromosomes can be copied in a complete way during cell divisions and how they are protected against degradation," which helped in understanding the very mechanism of the ageing of cells. It is thus assumed that the American scientists discovered both the presence of telomeres at the ends of chromosomes and the conclusion that their shortening leads to the ageing of cells.

16. Prospects

It is said that a theory is valuable only to the extent to which its conclusions allow experimental verification. On the other hand, a theory is expected to yield more than just a simple explanation of experimental facts [109]. When a theory that explains the general properties of living matter and how it differs from nonliving matter is created, this will signify the completion of the scientific revolution which was started by physicists, chemists, and biologists at the beginning of the 20th century but which is still incomplete. The achievements of Watson, Crick, Wilkins, and Franklin resonated so widely because their research led to clarifying the organization of the structure which lies at the root of heredity and is universal for all living organisms. Further investigations of the genome made it possible to prove that human DNA is to a great extent identical to the DNA of the *Drosophila* fly and other invertebrates. However, the principle of cyclic organization of DNA and proteins has been left outside the framework of theoretical analysis. The alpha helix was not discovered by Pauling through analyzing X-ray diffraction patterns. As Watson put it, "the essential trick, instead, was to ask which atoms like to sit next to each other" [67].

According to the modern physical theory of the structural organization of proteins, the fundamental principle is the statement that the spatial forms of peptides and proteins realized in biological conditions correspond to the most energy-preferred conformations of free monopeptides [110]. For Watson and Crick, a helix was merely the simplest and at the same time the most elegant configuration of a regular polymer molecule [67]. The discoverers of the structure of DNA considered it to be true because it was irresistibly beautiful: "The structure was too pretty not to be true" [67]. However, the question of why atoms prefer to be arranged in such a way that linear strands curl into the most energy-preferred single helix (in the case of proteins) or double helix (in the case of nucleic acids) remained unanswered.

The history of science always pays most attention to continually improved and continually developing theories. Sometimes these theories have a starting point and end point in history, but sometimes their history is such that they seem to have no starting point and tend to infinity because the interest in them never wanes with time, but only refills with new content. Scientists in different fields tried for a long time to formulate a generalizing principle which would hold true not only for living systems but for nonliving objects as well, and not only in some special areas of science but to our world as a whole.

In the 1930s – 1940s, the German biochemist Hans Krebs (1900 – 1981) suggested and substantiated metabolic cycles: the *urea* cycle (1932), and the *tricarbonic acids* cycle (1937) [111 – 114]. Later on, it was proved that many other cycles exist: the cycle of nitrogen oxide, and the cycle of the superoxide anion radical [115 – 119]. These cycles associated 95% to 97% of chemical elements present in the bodies of animals and plants with the system of cyclic transformations in the bodies of animals and plants because four atoms — C, N, O, and H — make up precisely this percentage of all chemical elements in organisms. The conclusion that could be drawn from this was: cyclicity lies not only at the base of metabolism in living organisms but equally at the base of the circulation of substances on Earth, including water and nitrogen and carbon atoms [46].

An analysis of the results of investigation and work on a specific scientific problem often stimulate certain qualitative images, assumptions, and hypotheses which later transform a series of unconnected guesses into a string of linked concretizations and generalizations [120]. To construct a theory, one often needs to select the most general concept of the subject of study and its intuitively comprehensible conceptual content. In such cases, there is always a subconscious, intuitive feeling which attempts to suggest a hint that the phenomenon one is attacking is a key to something big and completely new. R Feynman wrote at some point that we should extrapolate our knowledge into unknown areas; this is the only way for progress even if it is rather dangerous and unreliable [121]. This is how the *principle of cyclicity* has emerged from analyses of metabolic cycles involving the four main atoms present in living organisms (C, N, O, and H) [46, 119].

This principle made it possible to identity a general (cyclic) pattern in most various phenomena and processes that occur at practically every structural and functional level

in living and nonliving matter [46, 119]. This was a conjecture that made it possible to break through the tenets of the perfectly concrete field of biochemistry into a new field with a potential to join together various disciplines, including biology and medical sciences, physics and chemistry, and to identify the general principles that underlie practically all technologies ever developed by humanity. Why was the conjecture not formulated earlier? We know that the success of any research project is determined not only by the reputation of its author and the paradoxicality of the suggested concept. Success depends to a large extent on the results obtained by other researchers, and we know that these do not appear immediately or simultaneously [122].

It is common knowledge that the discovery of the Periodic Table of elements by Dmitry I Mendeleev in 1869 immediately confronted science with a number of questions. The main one was what causes this periodicity. A number of answers of different depth and generality have been offered. The most important feature, however, is that, in our opinion, the principle of cyclicity allows us to analyze each period of Mendeleev's table as one of the cycles. We have pointed out above that practically all planets and stars in our Galaxy and in the Universe are involved in cyclic processes. Some astrophysicists are of the opinion that there is a circulation of matter in cosmic space and thus our bodies incorporate the ashes of stars that died eons ago [46, 119].

According to current concepts, practically all chemical elements have been created and are being created in thermonuclear processes inside stars, and this leads to evolutionary changes in the state of stars [123, 124]. At the end of the 1930s, H Bethe and C Weizsäcker concluded that the mechanism of generation of energy in the Sun and in other stars involves cyclic nuclear reactions involving atoms of five elements (nitrogen, carbon, oxygen, hydrogen, and helium). The cyclic transformations of the five listed atoms are now known as the Bethe–Weizsäcker nitrogen–carbon cycle [46, 123, 124]. Incidentally, four of the elements in the Bethe–Weizsäcker cycle are among the chemical elements that form the basis of life and are themselves part of the circulation of matter in nature (the nitrogen, carbon, and water cycles).

Cyclic organization can be found in living organisms at very different structural and functional levels. Biologists know very well that metabolism is cyclic at the macromolecular level (biochemical cycles), at the cellular level (cell life cycles), and at the level of the organism (organismal life cycles). The main structural and functional elements in cells, i.e., *proteins* and *nucleic acids*, are built using a helical blueprint and, hence, comply with the cyclicity principle. The main principle of the compactization of DNA in chromosomes is also the principle of cyclicity, since a substantial fraction of DNA and histone proteins are curled into helix type structures. (Certain linker segments can be regarded as the proverbial exception that only confirms the general rule.) The myelin sheath surrounding axon and consisting of a lipid and protein layers forms a helical structure [5, 56]. A structure very similar to the helical structure of the myelin sheath is formed by glial cells around neurons in response to extreme stimuli [126]. Corneal lenses of many animals form a periodic structure whose pitch corresponds to the wavelength of visible light. The helix, thus, appears to be a conventional architectural element of very different biological molecules and structures [127].

All enzymes also function in a cyclic mode. All systems of homeostatic control have built-in feedback, and this means that the signal from the output of these systems is sent back to the input and thus transforms the system's operating conditions into cyclic ones. This cyclic organization manifests itself in numerous rhythms and periodic processes in living organisms. Self-oscillations of concentration are revealed in chemical, biological, and membrane systems [128]. Obviously, a cyclic pattern can be identified by studying how living systems are organized both in space and in time. Organization in space then manifests itself in helical structures, and temporal organization in the presence of rhythms and periodic processes.

Physiologists know that in order to learn how important one function or another is in an organism, one needs to switch it off and see what the consequences are. If we switched off all cyclic (or periodic) processes, then all biological rhythms would vanish, including periodic processes in the brain and in the heart. Hemoglobin would stop releasing and absorbing oxygen, blood circulation would come to a stop, as would all the pumps delivering certain ions into tissue cells and removing other ions from cells, and the heart would stop beating. All biochemical and energy transfer processes would stop, too, since enzymes operate in a cyclic mode. If all biological rhythms, all cyclic physiological and biochemical processes were switched off, life on planet Earth would come to an end. Therefore, both the topic of this discussion and the humans discussing this topic would disappear. Consequently, cyclic organization can be identified at various structural and functional levels in living organisms, in the biosphere, and in stellar matter. This is the reason why we believe that the most important aspect in biology and the medical sciences is the question of cyclic organization.

Cycles are inherent not only in all living matter and in the entire biosphere but also in the noosphere. Both the cognition and evolution of human society advance on a helical path. The philosophic laws of 'negation of the negation' and 'progress along the helix' (G Hegel) are essentially manifestations of the cyclicity principle. Historians analyze cycles in social activity and connect them with the cycles of solar activity [129].

A familiar cliche states that nothing speeded up technical progress as much as the invention of the wheel. In fact, the invention of the wheel had to be preceded by the birth of the idea of the wheel, later to be implemented as various mechanisms. Rotors, gears, wheels, pendulums, and everything capable of cyclic or oscillatory motion are inseparable elements of the machines and mechanisms ever designed by human hands. Alternating current, generators, triggers, and multivibrators cannot be imagined without an oscillatory or cyclic mode of operation. Electric and internal combustion motors also work in cyclic mode. We can thus say that practically all technologies ever created by humans include cyclic or oscillatory movements.

It can be expected that the *principle of cyclicity* will be recognized as one of the fundamental principles and used to analyze the cyclic organization of normal and pathologic structures and processes which are still treated as noncyclic: we still live in the world of linear concepts. The recognition of the principle of cyclicity may play the same role in the history of science as Mendeleev's Periodic Table played in chemistry. Mendeleev's Periodic Table is essentially cyclic, as each of its periods is a cycle. The strength of Mendeleev's periodic law, as we well know, lies in the fact that if one of the squares of the table composed of horizontal and vertical rows and columns has no element assigned to it, then chemists can ultimately discover the missing atom, being guided in their search by

predictions made on the basis of the position of the empty squares.

The strength of cyclicity principle in biology may signify that if we do not know all the elements creating a closed cycle of regulatory reactions, they may perhaps be identified by postulating the presence of closed cyclic structures. For instance, application of the cyclicity principle could have allowed a considerably earlier discovery of cycles in the electron-transport chain of mitochondria [129] and could have led to the diagram of cyclic functioning of the ATP synthase [130]. In the medical field, the strength of the cyclicity principle could be recognized and highlighted if medical doctors used this principle as a guide and sought individual damaged links that disrupt the functioning of the regulatory system as a whole, so as to normalize the work of both individual links and of the entire regulatory system at subsequent stages.

In L A Blumenfeld's opinion, scientific problems are either solvable or unsolvable [40]. Each branch of science forms a hierarchical construction. Each branch sits on statements that cannot be proved, since they belong to principles or postulates: 'laws of the first kind'. All other laws can be logically deduced from principles or postulates. The reduction of experimental facts or laws of the second kind to principles and postulates constitutes what we call 'explanation' or 'understanding'. Indeed, questions of the 'why' type can be asked until a certain principle is reached which allows stating that something happens to behave as it does because it obeys this very principle. For instance, we may conclude that DNA is organized as a helical structure because it obeys *the cyclicity principle*, and the helix in turn is a double helix because it satisfies *the matrix principle of copying information*. If the basic principles were always known in advance and always kept in view, many errors could be avoided.

In the mid-1950s, L A Orbeli once remarked apropos of an analysis of physiological processes: ''We hardly pay attention to the fact that all processes are cyclic and each process possesses its own cyclicity'' [6]. We have indicated at some point that even though facts are necessary, simple accumulation of experimental data does not add to *understanding* or produce *a theory*. Furthermore, there are stages in our cognition of Nature when the factor of greatest importance is not the facts themselves but *what* these facts signify, or rather that more general something to *which* they point. In other words, the task of paramount importance is to single out the most general and the most meaningful thing which may happen to be that central piece that kept escaping us. Not understanding this *central piece* thwarts our efforts to advance the cognitive process. We would like to emphasize once more in conclusion that cyclic structures and processes belong not only with physiology, biochemistry, or some other special branch of science; cyclic processes and structures have a very direct relation to the world as a whole because Nature establishes its unity in the cyclic organization. Consequently, our understanding of the solvable problems of the world in which we live may be appreciably extended by expanding the system of fundamental principles and adding to them *the cyclicity principle*.

17. Conclusions

The idea of humankind transforming its environment was first formulated in the works of G L Buffon and other 18th-century French scientists [131, 132]. 'Natural Philosophy', as it was shaped by these scientists in the European culture of the New Time, treated Nature as a world of nonliving objects with which one can and ought to work and which need reconstruction, modification, and practical redesign [133]. The well-known motto was: ''we should not wait for nature to gift us her blessings; our task is to grab hold of what she has'' [134]. These words reflected the ruling paradigm even in the first half of the 20th century, aimed at 'subjugating' Nature. This paradigm brought success to all natural sciences, including physics, beginning with the birth of the theory of relativity and quantum mechanics and ending with space flight and the development of atomic and thermonuclear weapons. A new paradigm started to take shape in the 20th century as a result of progress in biology, chemistry, and thermodynamics of open systems, as well as philosophical rethinking of empirical data; this paradigm assumes that we live and act inside the biosphere where all processes are interrelated, and therefore we need to treat the world as an organism and not as nonliving nature [135, 136]. This paradigm gained popularity not only among scientists but also among the general public as it was reflected in numerous works of art, in science-fiction books, and in movies. What role then has molecular biology and genetics played in the formation of the reformed social understanding and growth of the paradigm in which people should consider the world as a biosphere?

There can be no doubt that unraveling the secret of the structure of DNA caused a revolution in natural sciences and led to a number of new discoveries without which modern science cannot be imagined. Further genome studies showed that human DNA is very close to that of other living organisms. The catchphrase that gained popularity was: *conclusions valid for the Drosophila can be applied to the Elephant*. Watson and Crick's discovery was followed by an explosion of genetic studies. The arrival of such methods as the polymerase chain reaction, molecular cloning, and sequenation would be impossible without knowing the DNA structure. Knowing this structure, in turn, helped in understanding the mechanism of replication (doubling) of DNA and thus in establishing how genetic information is transmitted from generation to generation. The solution to the problem of organization of the hereditary apparatus of cells not only constituted the starting point in the unfolding of a new science — molecular biology — but also provided impetus to spreading the idea of a humane attitude to all biological components of the biosphere of planet Earth.

We wish to draw attention once again to the fact that *the principle of cyclic organization of DNA and proteins* was somehow shifted aside in the investigation of the structure of nucleic acids and proteins. If it is true for 21st century biology that task No. 1 is to identify the most general and essential factors that form the basis of life processes in living organisms, and to find more general principles of organization which predetermine the natural development of living matter and the establishment of links between individual phenomena and fundamental principles, then there can be no doubt that all of us need to pay very special attention to cyclic structures. It is possible that *cyclicity* is that very absolute factor, that universally significant and invariant attribute of each living and nonliving system. We are of the opinion that this may have paramount importance for identifying the most general and the most significant things that we do not fully understand. This incomplete understanding of the main factors may prove to become a serious

obstacle on the way to further cognition of Nature. In view of this, those who think that cyclicity is only a matter for philosophy but not for physics, chemistry, biology, and medical practices are very much in error, because 'no cycles' implies 'no life'. It should be reaffirmed that, as for the degree of its generality, *the cyclicity principle* can be put in the same row with *the atomic principle* of the structure of matter [46, 120], and also with the categories of space, time, and motion [46, 119, 120]. Indeed, everything that we know about matter, space, time, and motion is in one way or another linked to cyclicity.

It is said that continuous evolution of a theory is meaningful only as long as the theory retains a core of 'historically invariant content' that survives for a relatively long time [120]. Physicists often invoke as an example the concept of the atom, which evolved for more than 2000 years before reaching the status of the theory of the atomic structure [120]. The history of the problem of cyclicity that refuses to go away is at least as long, even though we know much less about it than about the atomic structure of matter. In reality, the unified existence of living and nonliving Nature expresses itself not only in the atomic structure of matter but equally in its cyclicity which manifests itself at all structural and functional levels. Our concept of the world tells us that *cyclicity is one of the common fundamentals for living and nonliving systems* and that *the general theory of cyclicity* may grow into that unified theory that carries the historically invariant content and constitutes the subject of research for a variety of specialists over many centuries. Such *a general theory of cyclicity* could offer a basis for numerous generalizations in a number of branches of knowledge and would serve as a foundation for the progress of social consciousness and a drastically new humane attitude towards the phenomenon of life, living organisms, and a wise and responsible approach to developing various technologies on planet Earth. The words of Henri Poincaré are a proper conclusion to our paper: ''Each generalization suggests to some degree a belief in the unity and simplicity of nature. As to unity we cannot meet here any difficulties.... We should ask ourselves the question: How is nature unified? rather than the question: Is nature unified?''

18. Appendices

I. Rosalind Franklin: talent and fate

It would be fair to say that the discovery by Watson, Crick, and Wilkins is the best known discovery, not only in 20th century biology but in science in the entire 20th century. Salvador Dali put the DNA structure on one of his paintings, and one of Niels Bohr's former students wrote to him in Copenhagen: ''Here in Cambridge we had perhaps the most outstanding event in biology after the publication of Darwin's book: Watson and Crick unravelled the structure of the gene!'' [44, 72]. Unfortunately, Rosalind Franklin did not live to see the moment of general recognition. It was only much later that the science community learnt about her courage and about her devotion to science [75].

Rosalind Franklin learnt about her cancer in 1956 but continued to work, without complaints, almost until her death, striving to bring her experimental techniques to perfection. All this time she was going through chemotherapy in Cambridge; she practically lived in Crick's house, having become a close friend of Crick's family after 1953. Franklin sincerely believed that medical science and doctors would find a cure for her illness. Rosalind Franklin was seen in her laboratory for the last time three weeks before her death. She died on 16 April 1958 at the age of 37, three years before the work on the structure of DNA was recommended for the Nobel Prize. It was the day when the model of the tobacco mosaic virus, representing the results of a new work by Franklin and her colleagues, was to be demonstrated at the World Exhibition in Brussels. Watson remembered Rosalind Franklin in his book *The Double Helix* [67] published 15 years later, and pointed to her very significant contribution to the discovery of the structure of DNA.

In the opinion of historians of science, much in the research conducted by Wilkins and Franklin at the beginning of the 1950s is still unknown. There is no doubt that working primarily as physicists-methodologists, concentrating on bringing their experimental technique to perfection, they shifted the priorities away from the biological aspects of studying DNA — just those aspects which could clarify the principles of the organization and the specific features of the physical design of this macromolecule. In contrast, Crick and Watson were obsessed with the principles of organization of DNA. As a team, they brought together the knowledge of physics, chemistry, and biology, which predetermined their success [44, 72, 75].

II. James Watson, post-Nobel Prize

It is said that accident is one of the forms in which necessity manifests itself. As a rule, it takes some time in science before a young researcher who has the courage to discover something new becomes famous. Recognition is not unlike retarded potential in physics. It is no secret that Director of the Cavendish Laboratory W L Bragg dreamt of the day when Crick would leave the Laboratory, and the brilliant E Chargaff continued to refer to Watson and Crick as 'scientific clowns,' even after their paper was published in *Nature* [67].

How could it happen that a 25-year-old postdoctoral student who had spent less than eighteen months in his field of research became an author of a paper presenting results for which the Nobel Prize was awarded? What happened? A gift from the gods or historical justice? Wonderful intuition, a sharp mind, and the ability to look at a problem from an angle possible only in a flash of inspiration allowed James Watson to become that very scientist whose name will be forever associated with the model of the structure of DNA.

A year after publishing the paper in *Nature* in April 1953, Watson was appointed Senior Researcher of the Chair of Biology at the California Institute of Technology in Pasadena (California). In 1955, when he worked as assistant professor of biology at Harvard University in Cambridge (Massachusetts), fate again brought Watson and Crick together, and they conducted joint research until 1956. In 1958, Watson was appointed adjunct professor and in 1961, full Professor. In 1965 he wrote a book *Molecular Biology of the Gene*, which became one of the best and most popular textbooks on molecular biology [61]. In 1968, Watson became Director of one of the then largest centers of molecular biology research — Cold Spring Harbor Laboratory. His work then shifted largely to neurobiology and to studying the role of viruses and DNA in cancer. In 1968, he married Elizabeth Lewis, who worked as an assistant in his laboratory. They had two sons; the family settled in a 19th-century house built on the territory of the university campus.

Molecular biologists from all over the world started coming to Watson's Cold Spring Harbor Laboratory. Staying always in the thick of advancing science, Watson was invariably able to combine research and teaching. For many years he lectured to students at Harvard University and Redcliffe College. Watson, with his excellent ability to present the material in a well-structured, clear, and systematic way, included in his lectures both the most important concepts that served as starting points for the progress of molecular biology, and the latest achievements in science. He is still famous for his short and simple manner of speaking, achieving the result he aims at. He has never been afraid of attacking problems which seemed unsolvable in the 20th century. Watson is an interesting person and a witty speaker; his lectures, even on very serious subjects, are invariably interspersed with jokes and aphorisms. Watson's advice to students were and still is: ''Avoid tiresomeness,'' and ''Avoid boring people.'' Watson's love of jokes and biting remarks continues to attract journalists, TV hosts, and fans in many countries. In fact, Watson's jokes and unguarded opinions damage his reputation again and again. Thus, in 2007 a scandal exploded in the USA when, outlining the cultural and historical analysis of development in the Americas, Europe, and Africa, Watson incautiously linked the apparent differences not with natural phenomena but with genes — which caused much irritation in certain powerful echelons.

J Watson has received an enormous number of honors, has received degrees *honoris causa* from 32 universities, and has published nine books: *Molecular Biology of the Gene* (1965, 1970, 1976, and 1987), *The Double Helix* (1968), *The DNA Story*: *A Documentary History of Gene Cloning* (1981), *Molecular Biology of the Cell* (1983, 1989, and 1994), *Recombinant DNA: Genes and Genomes — A Short Course* (1983, and 1992), *A Passion for DNA* (2000), *Genes, Girls, and Gamow: After the Double Helix* (2002), *DNA: The Secret of Life* (2003), and *Avoid Boring People: Lessons from a Life in Science* (2007).

However, a scientist's world is not limited to their published work, their students, and like-minded colleagues. First and foremost, it is the world of their fruitful ideas and initiatives. In 1988, Watson became the initiator and first director of the Human Genome Project — the biggest international research program at the end of the 20th century, first aimed at sequencing human DNA, but then at complete decoding of the human genome. Watson's closest collaborators in this project were Francis Collins and Craig Venter. Essential contributions to the decoding of the genome were made by W Gilbert, F Sanger, P Berg, and A D Mirzabekov. Berg, Gilbert, and Sanger received the Nobel Prize in Chemistry 1980 for their contributions concerning the biochemistry of nucleic acids and determination of base sequences in them. The work of Watson and his colleagues greatly influenced research in molecular biology on a global scale. Academician A A Baev (1904 – 1994) was an enthusiast of deciphering the human genetic code in the USSR and then in Russia. In 1988, work was started in Moscow on the Human Genome Program under the auspices of the USSR Committee on Science and Technology. Through the work of scientists in the US and the USSR, research centers began work in 1989 – 1990; later on, these centers (supported by science centers of other countries, mostly the United Kingdom, France, Germany, Japan, and China) joined to form the international organization for studying human genome (the Human Genome Organization — HUGO). For several years the Russian Academician A D Mirzabekov was HUGO Vice President. It was estimated that the determination of the complete structure of the human genome cost more than six billion US dollars over a little more than ten years. The Human Genome project became one of the costliest in biology. In the opinion of a number of biologists, as voiced by the British scientist Michael Dexter, finding the complete structure of the human genome is one of the most important achievements of humankind, reaching in its significance beyond the launch of humans into extraterrestrial space or landing on the Moon. We live in times when the predictions of the outstanding physicists of the 20th century Niels Bohr and Erwin Schrödinger (that the most exciting insights into the secrets of Nature will become the prerogative of biology, not physics) are coming true. It is therefore difficult to overestimate Watson's contribution as researcher, science organizer, and human being to our understanding of Nature. When we discuss James Watson, there is no need to repeat that time is the supreme judge in all scientific matters. Watson's name has forever found its place alongside the names of Newton, Darwin, Einstein, Bohr, and Schrödinger already in his lifetime.

III. Francis Crick, post-Nobel Prize

In 1953, Crick completed his thesis on X-ray diffraction analysis of protein structure and received his PhD degree from Cambridge. In 1954, he studied the structure of proteins at the Brooklyn Polytechnic Institute in New York and lectured at various universities in the USA. Having returned to Cambridge in 1955, he continued his research at the Cavendish Laboratory, focusing it on deciphering the genetic code. Originally a theoretician, he started to study genetic mutations, together with Sydney Brenner, in bacteriophages (viruses that infect bacterial cells).

By 1961 three types of RNA had been discovered: messenger, ribosomal, and transport. According to Crick's theory, messenger RNA reads genetic information off DNA in the nucleus of the cell and transports it to ribosomes (entities where proteins are synthesized) in the cellular cytoplasm. The transport RNA delivers amino acids to ribosomes. The interaction between the messenger and ribosomal RNA takes care of joining amino acids to form protein molecules in the correct sequence. In 1962, Crick was appointed Head of Biology Laboratory at Cambridge University and foreign member of the Salk Institute in La Jolla (California, USA). In 1977, he moved to San Diego, having been offered a professorship there. At the Salk Institute Crick worked in neurobiology, studying in particular the mechanisms of vision and dreaming.

In 1983, in collaboration with the British mathematician Graham Mitchison, he suggested that dreams are a side effect of a process by which the brain removes excessive or useless associations accumulated during the state of being awake. Crick and Mitchison hypothesized that the function of this form of 'reverse learning' or 'unlearning' is to prevent overloading of processes in nerve networks. In his book *Life Itself: Its Origin and Nature*, F Crick pointed to the amazing similarity of all forms of life that except for mitochondria, the genetic code is identical in all the living objects studied at present [137]. Referring to discoveries in molecular biology, paleontology, and cosmology, Crick assumed that life on Earth could have started with the arrival of microorganisms, widespread in cosmic space, from another planet; Crick and

his colleague Leslie Orgel called this theory 'directed panspermia' [137, 138].

IV. James Watson's lectures in Moscow in 2008

In June–July 2008, James Watson paid a visit to Russia on the invitation of the Presidium of the Russian Academy of Sciences, supported by Dmitry Zimin's Dynasty Foundation of Non-Commercial Programs; the visit was on the occasion of the 80th anniversary of the birth of this outstanding scientist and the 55th anniversary of the creation of the DNA double helix model. There is no doubt that James Watson is one of the most influential contemporary scientists. His name will live forever in the history of science alongside the names of other outstanding scientists.

James Watson visited Russia more than once and was hosted by many of our leading molecular biologists. He was elected a foreign member of the Russian Academy of Sciences (RAS) and received the highest distinction for a scientist in Russia — the M V Lomonosov Gold Medal. On 30 June 2008, Watson gave the lecture "Can DNA show us how to cure cancer in our lifetime?" in the conference hall of the V A Engelgardt Institute of Molecular Biology of the RAS (IMB). In this lecture, James Watson discussed the history of studying DNA in the context of studying tumorous cells from the first discoveries to the so-called era of the genome.

Ever since the time of the discovery of the double-helix structure of DNA and until the launch of the Human Genome project, science concentrated on genes which destroy the normal functioning of cells of the organism and produce malignant new growth. Watson pointed out in his lecture that despite the identification of oncogenes causing cancer and despite intense research in developing anticancer drugs, we still have no reliable method of curing cancer. It is not impossible that this failure is linked in an unknown manner to the ability of the tumorous cell to modify its DNA. At the same time, Watson thinks that there are reasons to believe that a combination of high-resolution genomic studies and extended clinical testing may in the near future lead to DNA-biopsy — a technique that will hopefully allow prescribing the 'correct' medicine to each specific patient, and in the end to curing this disease. Watson ended his hour-and-a-half talk at the IMB with a joke: "I hope next time I visit Moscow the genome of Russia will have been decoded." On 30 June 2008, the conference hall at the IMB was too small to make room for all those who came to hear the words of the famous scientist. The papers later reported that "the IMB main lecture hall has seen just about everything but even the oldest in the audience could not recall anything like this unprecedented 'sold out' performance." On 3 July 2008, Watson gave the lecture "DNA and the Brain. In search of Mental Disorder Genes" in Moscow, at the House of Scientists on Prechistenka. Three questions were central:

(1) What role do genes play in mental disorders?

(2) What results could be achieved by reading the DNA of mentally ill people?

(3) What breakthroughs can be expected in the area of psychiatric genetics?

Several thousand representatives of the science intelligentsia and journalists from TV and other media came to this meeting with one of the great scientists of our era. The queue at the House of Scientists was several hundred meters long. Such scenes are usually observed when a visiting exhibition of paintings from the most famous museums opens in the Museum of Fine Arts nearby. The House of Scientists, with a conference hall capacity greater than that at the IMB, equally failed to accept everyone who wished to see and hear James Watson. Professor S P Kapitsa, whose task was to produce a TV program on Watson, managed to squeeze in, but only with the greatest effort. Some listeners could only reach the foyer where a display screen transmitted Watson's presentation. Most of the people had to wait for Watson in the inner courtyard of the building. A group outside the building listened to the lecture through speakers installed on the balcony.

In the first part of the lecture Watson outlined his path in science and how he organized work in his laboratory. He said that all his life after 40 he had been selecting staff members. He always favored active and promising young people over the well-known and the famous, rarely rejecting candidates and taking fast decisions: research needs lots of people, there is work for everyone. In his career in research he always did everything rapidly. His advice: one should never undertake anything unless one knows there is a chance of shooting to the very top; never work hoping to become 'number 10', but strive to be 'number 1' and nothing less; if one only becomes 'number three', well, one should definitely be happy because 'number three' is also very good. At the beginning, the laboratory that he headed was very poor and had no tenured researchers. Watson acted as a sort of assistant director. He never told those he hired which science they need to work in: he tried to give them maximum freedom. This was his principle: give people the opportunity to take their own decisions. He simply helped them to solve their problems. His office was always open and he tried never to tell people 'No'. At the same time, he tried to make himself unnecessary, to such an extent that if he decided to spend a year in Europe, no one should even have noticed it.

In the second part of the lecture Watson talked about his current research interests which concentrate on genetic control of such mental disorders as autism and schizophrenia. It was possible to hypothesize for quite some time that such tragic psychic disorders as autism and schizophrenia have a hereditary component. However, earlier studies of familial heredity refused to follow a simple Mendelian interpretation based on dominant, recessive, or gender-coupled genes. In fact, the example of observation of monoovular twins makes it possible to conclude that genes must play an important role in mental disorders. After the Human Genome project was completed in 2003 and low-cost high-productivity technologies of DNA sequencing were introduced, it became possible to directly read the DNA sequences of mentally ill people. Watson described new data obtained at the Cold Spring Harbor Laboratory, which demonstrated that these new techniques had already led to revolutionary transformations in psychiatric genetics.

The choice of the problem was not accidental. One of Watson's sons has a mental disorder. In Watson's words, many genes are linked to the progress of schizophrenia, including those which take part in the formation and development of the central nervous system. Watson said that he and his colleagues had studied only about 200 cases and observed certain changes in the number of copies of genes in people with schizophrenia that they never observed in normal people. In most cases, these changes occurred in genes which control the functioning of the nervous system. Watson believes that about 30,000 cases of schizophrenia sufferers need to be studied before general patterns can be identified.

Watson's talk at the House of Scientists. Moscow, 3 July 2008.

He also explained that it currently costs about 1000 dollars per patient in cases where DNA was collected for some other purposes. This is the cost of just the work of him and his colleagues. Hence, 30,000 cases means 30 million dollars, a huge amount of money. Where do they get the funds to spend millions of dollars? Not from the government; they are donated by parents whose children are autistic or mentally ill. Autism research is supported by the fund set up by mathematician Jim Simons, who left the Mathematics Department at Stony Brook in order to become a financial investor. Last year he alone invested 3 billion dollars. His daughter is autistic and he supports our work. There is another family, the Stanleys, whose son has bipolar disorder and they have already donated nearly 200 million dollars for the study of schizophrenia and bipolar disorder. This is why James Watson says that studying the molecular foundations of pathology at this moment is encountering serious difficulties, while decoding genotypes of people suffering from schizophrenia is very expensive.

In Watson's opinion, starting to model schizophrenia on mice and rats will only become possible five to ten years from now. Watson said that until very recently, he and his colleagues had tried to identify the genetic factors which caused these disorders, and to find interrelations between them. What they found was a special segment in the 16th chromosome: genetic modifications in this segment produce autism or schizophrenia, but may have no consequences. Why does this happen in this way? What is the mechanism involved? Watson and his colleagues are now trying to find answers to these questions.

It was not only the conference hall and the foyer, but also the inner courtyard of the House of Scientists that was packed full from the first to the last minute of the lecture. After the lecture ended, James Watson emerged on the balcony. It was obvious that he was surprised and deeply moved by the level of attention from the Russian public. The lucky few in the conference hall of the House of Scientists, as well as those in the foyer and in the courtyard, were able to ask their questions. In the end, somebody cried out in English: "Do come back, Mister Watson!"

In addition to presenting these two lectures, Watson gave during his academic visit to Moscow a TV interview to S P Kapitsa and visited Moscow State University, where he received the mantle and badges of Honorary Professor of the University.

V. What conclusion can we draw after analyzing the history of the discovery of DNA and James Watson's lectures?

In the past we assumed that the "*human genome is the encyclopedia of life written in four letters*" [44]. We are not so sure any more that the current language of biology, chemistry, physics, and mathematics is adequate for formulating a complete explanation of the structure and functioning of a cell, or organ, or organism. Will it be necessary to develop principally new approaches and new branches of science? Some contemporary scientists believe that the theoretical analysis and description of biological phenomena will not require creating radically new physics. However, the history of science demonstrates that it evolved — and continues to evolve — on the one hand, in harmony with its profound inherent inner logic, and, on the other hand, through introduction from the outside of tested approaches, problems, ideas, and solutions which were not, and are not, found (not necessarily) in the field of view of habitual, even traditional, fields of science. Discussing the successes of molecular biology, we inevitably understand that they could hardly be possible without interaction between biologists and physicists, chemists, mathematicians, and cyberneticists. At the moment, many scientists are convinced that the gap between biology and psychiatry is so wide that it cannot be bridged by any modern formulations, concepts, or theories which try to connect that *which can be recorded and measured* with that *which people do without trying to figure out* how in the end they achieve it all [40]. What could be the way out of this quandary?

Once in the 1970s, two well-known scientists — electrophysiologist Mikhail Nikolaevich Livanov and biophysicist Lev Aleksandrovich Blumenfeld — had a discussion about this subject at a seminar held at the USSR Academy of Sciences Institute of Biological Physics in Pushchino. L A Blumenfeld described the progressive evolution which produces gradually higher-organized complex structures capable of task-oriented actions, and advised his listeners to have a good look at the fundamental work of Lev S Berg, *Nomogenesis, or Evolution Based on Non-Random Regularities* [11]. L A Blumenfeld suggested that Berg's principal concept can be formulated like this: biological evolution obeys strict laws, in contrast to Darwinian evolution which is based on random events. Berg essentially assumed that the central problem in biological evolution is the compulsory emergence of a teleological, task-oriented response to a stimulus. In other words, teleological patterns form the fundamental property of life. As L A Blumenfeld put it, "This work implies that there must have existed an original blueprint for creation of life. A monkey randomly hitting the keys of a typewriter would never produce *Hamlet*." L A Blumenfeld completed his lecture with the following words: "I know two things. First. I know that I have free will and a soul. Second. I do not know the principles of interaction between the soul and the body but I suspect that no one knows it and they will forever remain unknown. What are we to do in this situation?" — that was his question to M N Livanov.

Livanov's reply to this was: "In the 2nd century *A.D.* Marcus Aurelius wrote in his notebook the following brilliant remark: "The world is either the fruit of design or a consequence of accident. If the latter is true, the world is amazingly regular and beautiful." As for your question, Lev Aleksandrovich, you know the answer without my telling you anything: we need to continue working as diligently as ever...."

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