PHYSICS OF OUR DAYS

Physics and biology

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When a physicist first turns to biological structures and biological processes, they seem to him hopelessly complicated and intricate. But this is an illusion. It suffices to compare the situation in biology 10—20 years ago and today to see the fruits of a phenomenal progress. The problems that seemed unsolvable have been transformed into a class of scholastic truisms. Application of the arsenal of physical instruments and methods, and above all, of physical ideas, has made it possible to formulate and solve any problem of natural science. The doubts that physical laws are fully applicable to living matter, as expressed by such noteworthy physicists as Schrödinger and Bohr, have not been borne out. All biological molecules and biological processes fully obey the laws of quantum mechanics and statistics.

I shall take up only briefly an already elapsed stage of biophysics: the founding of molecular biology during the past 20 years. This field has been treated in such great detail in popular magazines and even in newspapers that I shall touch on it only briefly, and shall concentrate attention on unsolved problems, on problems of the near future. There are three such fundamental problems now in the field of biology. First, they include the problem of morphogenesis, i.e., formation of supermolecular structures, cellular organelles, and membranes from various classes of molecules, and the problem of their structure and function. Second, there is the problem of differentiation and development of the embryo of a complex organism, or the so-called ontogenesis. Third, there is the problem of neurobiology, or the mechanism of operation of the nervous system and the decoding of the neurobiological code, and as its final goal, the knowledge of the mechanism of human consciousness.

All three of these problems are very far from solution. Yet the ideas and methods of physics are ever more successfully and effectively being applied to them as well. Hence it is of interest to take a "bird's eye" view of the state of matters, and at least to try to formulate the most important problems. I make the reservation that I shall not henceforth distinguish between physics and chemistry, considering the latter to be merely a branch of molecular physics. Undoubtedly, all chemical phenoma can be understood and interpreted by means of the Schrödinger equation. Empirical solution of many problems is more economical than calculation only because of technical, i.e., computational difficulties. There are no fundamental limitations here. One can see this well now, when use of computers has made it possible to calculate the properties of complex many-electron molecules. Hence, when I shall say "physics", this will mean "physics and its chemical applications."

After these preliminary remarks, let us enter into the topic, and first take up the past stage. As we know, biology has greatly lagged in its development behind the exact sciences. Thus, physics became an experimental science even in antiquity, while biology remained an almost exclusively observational science until the 18th—19th Centuries. Even such founders of biological science as Darwin and Mechnikov were exclusively observers, rather than experimenters.

Two branches of biology began to resort to experimentation and measurement earlier than other branches. First of all, there was genetics. Mendel initiated exact statistical experimentation and quantitative conclusions from it, followed by the whole constellation of geneticists: Morgan, Weisman, Sturtevant, etc. In addition, biochemistry was developing as a branch of chemistry. Beginning with Lavoisier, Boussingault, Liebig, and Emil Fischer, quantitative study began on the balance of different substances in living organisms and their composition. Quantitative laws arose thereby. Like genetics, biochemistry preceded biology as a whole. It is no wonder that the problems arose precisely on the border between genetics and biochemistry that physicists attacked with all their weaponry of ideas and experimental means that had been created by the scientific-technological revolution of the first half of our century.

How shall we formulate the main problem or problems that have been thus far solved by molecular biology? We can list them as follows: biopolymers, i.e., proteins and nucleic acids, their structure and function, as well as the mechanism of heredity and variability in living nature.[1] We see the methodology of physics even in the formulation of the problem. Physics proceeds from the structure of matter, from the structures of the two most important types of molecules that comprise living beings, the proteins and the nucleic acids. While they seemed hopelessly complicated even 30 years ago, they have become understood and studied in all details in the historically insignificant span of 15 years, owing to application of x-ray crystallographic analysis, spectroscopy, radiospectroscopy, electron microscopy, isotopic methods, and first of all—the ideas of modern molecular physics, statistics, and quantum mechanics.

Understanding of the structures of biological molecules quickly led to deciphering their functions. In 1953, the famous study of Watson and Crick gave a theory of the structure of the nucleic acids. DNA proved to be a polymer whose chains form a two-stranded helix wound on a cylinder 15 Å in diameter (Fig. 1). The polymer chains consist alternately of molecules of sugar and phosphoric acid. The so-called nitrogen bases (adenine, guanine, thymine, and cytosine) are attached laterally to the chains. They fill the entire inner cavity of the cylinder like a stack of coins.

The most important feature in this structure is the exact correspondence of the side groups in the two opposing chains. Opposite adenine is always thymine, and

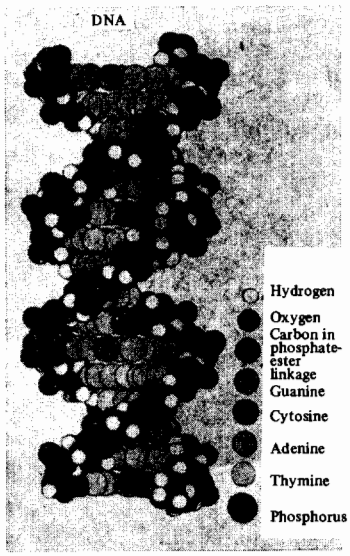

FIG. 1. Molecular model of the Watson-Crick double helix. The inner cavity of the helix is filled with the side groups, or purine and pyrimidine bases. (The model is built from x-ray structural data.)

opposite guanine is cytosine. The point is that this is the only combination that permits formation of hydrogen bonds between the two chains (Fig. 2). Hence we get the Watson-Crick principle, the principle of supplementation, or complementarity. One of the two chains fully defines the other complementary chain. When the chains separate, monomers are adsorbed on the liberated nitrogen bases with exact obedience to the Watson-Crick principle: adenine on thymine, cytosine on guanine. When the monomers are combined into a chain, we get two absolutely identical chains from one two-stranded chain (Fig. 3). The very structure of DNA contains within itself the principle of replication, i.e., transfer of inheritable traits from mother to daughter cell.

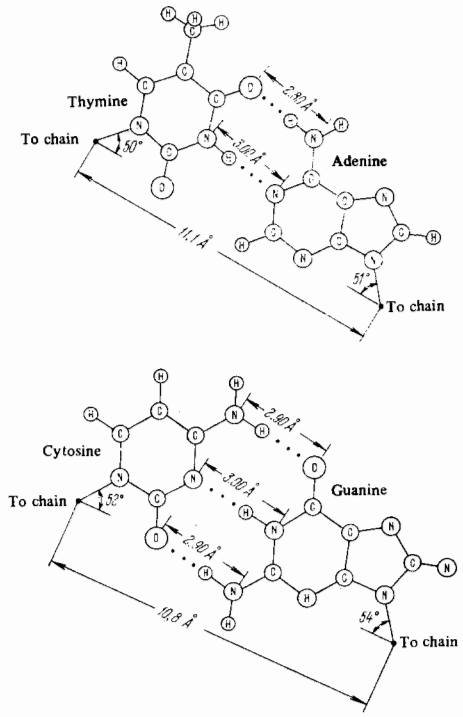

FIG. 2. Complementarity of the side-groups (diagrams of the base-pairing).

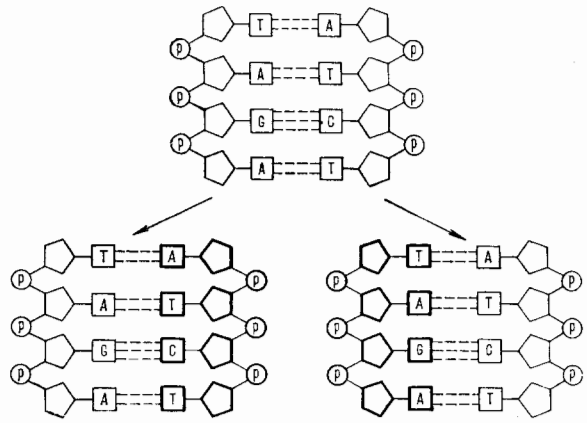

FIG. 3. Diagram of the semiconservative replication of DNA.

They further showed the existence of a genetic code that relates the linear sequence of nucleotides in nucleic acid to the linear sequence of amino acids in a protein chain. As we know, there are 20 irreplaceable amino acids, but 4 nucleotides. This is about the same situation as in writing the letters of the alphabet using the Morse code. The latter uses two symbols, the dot and the dash. Hence, to represent the 32 letters, we need sequences of several signs of the Morse code. This will be the coding number. The genetic code has the coding number of three. One can make 64 codon triplets from the four nucleotides to represent the 20 amino acids. It has been established that the code is degenerate. That is, several codons belong to one amino acid.

The processes of synthesis of nucleic acid and of protein in themselves give us examples of template syntheses. A template exists (as in book printing) that imposes a strictly determined sequence of nucleotides in the nucleic-acid case, and of amino acids in the protein case. In template synthesis, one polymer chain is assembled on another. For the nucleic acids, nucleotides are assembled on a polynucleotide chain. The molecular forces that control this process are the hydrogen bonds between the bases: adenine and thymine, guanine and cytosine.

In protein synthesis, amino acids are assembled on a polynucleotide template. This is carried out by means of the intermediate links of small polymers, or transport RNA's. Each transport RNA combines with its own amino acid, while the middle of its chain, which forms a fold, contains a triplet of nucleotides, which is the so-called anticodon. This anticodon combines with the complementary triplet of nucleotides on the template, which is the so-called codon (Fig. 4). This is how the step-by-step assembly of amino acids into a protein chain occurs. The information on the structure of the protein is printed in the polynucleotide chain with its sequence of codons. In this case also, the molecular forces that determine the operation of the template are hydrogen bonds between the bases. The Watson-Crick principle is the universal law by which nucleotides interact, and on which are based all of the known template syntheses in biology.

It has further turned out that one can easily explain the variability of organisms, i.e., the nature of mutations. This involves chemical modifications of DNA that occur under the action of radiation and chemical muta-

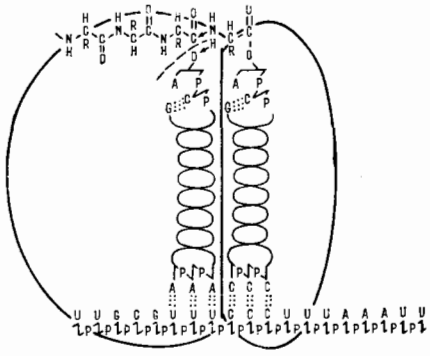

FIG. 4. Diagram of an intermediate stage in protein synthesis. One can see sites in the two subunits of the ribosome that contain two molecules of transport RNA that are partly helical. At the bottom of the two molecules are shown the triplets, or anticodons, which are bound by hydrogen bonds to the complementary triplets, or codons, in the messenger RNA chain. At the top, the left-hand tRNA bears at its terminus an (incomplete) protein chain, and the right-hand tRNA bears the next amino acid, which has been selected in agreement with the anticodon CCC. Each amino acid corresponds to its own specific transport RNA, which performs the selection of amino acids. The next step will be chemical reaction of the next amino acid with the peptide chain; the left-hand tRNA is released and goes back into solution, while the right-hand tRNA with the protein chain transferred to it moves one step (one triplet) from right to left. Then the next tRNA bearing the next amino acid is adsorbed from solution, etc.

gens. And spontaneous mutations, which are the motive force of evolution, are simply random errors, or "thermal" noise in the copying of DNA. Thus, the fundamental function of the nucleic acids, which is the transfer of genetic information from the nucleus to the proteins being synthesized in the cytoplasm, has been thoroughly elucidated.

As for the functions of the proteins, the major one of which is catalytic or enzymatic, they have been elucidated to a lesser degree than for the nucleic acids, although people have been able to understand the fundamental principles from understanding the functioning of a few of the best-studied proteins: hemoglobin and ribonuclease. Mastery of the enzymes promises in the future a true revolution in chemical technology.

The knowledge of the proteins and nucleic acids has been crowned by their complete laboratory synthesis. A special automatic machine was invented for synthesis of proteins, which well embodies the 20th Century in science. The simplest genes have also been synthesized jointly by the methods of chemistry and biochemistry. In the enzyme field, it has been possible for the first time to synthesize an artificial, i.e., model polymer that accelerates a chemical reaction by 10—12 orders of magnitude, i.e., like a protein.

Thus, a giant breakthrough has been made in this field of science. The representatives of physics have had a vast, decisive importance in it. I shall cite only a few names. In the structural analysis of proteins, the first contribution was that of Bragg and his closest students Perutz and Kendrew, and also that of Paulding and Bernal. All of this group of eminent physicists laid the groundwork for protein structure analysis. In the structural analysis and in the study of the functions of the nucleic acids, other physicists have played the decisive role: Crick and Wilkins, as well as Delbruck, Benzer, Brenner, Stent, and Geren. Finally, the first distinct formulation of the problem of the genetic code is due to Gamow. I must also mention Schrödinger, whose book, prophetic in many ways, What Is Life?, was written as early as 1944, and gave the first impulse to arouse the interest of many eminent physicists in the problems of biology, in particular, genetics.

One may ask the current situation in molecular biology after such brilliant advances. I did not wish to create the impression that everything in it is now done and finished. No, molecular biology is yet far from being finished. Many interesting details remain in it for development, in particular and especially, problems that promise much in practice, for the satisfaction of human needs.

I might compare the situation in this field of science with that in solid state physics. Every physicist knows that in principle all phenomena in a solid can be understood and calculated by using the equations of quantum mechanics and statistics. No one thinks that we can expect a revolution in this field, but the number of interesting details that demand study and the number of varied possibilities for applications are as yet inexhaustible. Hence, many distinguished workers gladly pursue this field of physics. The situation is similar now in molecular biology and molecular genetics. We need yet to understand in all details the processes of mutagenesis and recombination, and they are extremely important in practice. We need to understand thoroughly the enzymes, and to learn to make models of them, in particular, for practical purposes. A new, very interesting field has arisen that is called "gene engineering." Since one can synthesize genes at will in a test tube or extract them from the chromosomes of living organisms (laboratories are already dealing with an entire series of "pure genes" in weighable amounts), the problem arises of introducing them into the chromosomes of cells of bacteria, plants, and animals in order to adapt them there and to make them transmit to the cells the so-called exogenous (foreign) information. Solution of this problem can permit us to solve economic problems that are fantastic in scale.

I shall give merely several examples. As we know, certain bacteria contain genes that code for production of the enzyme nitrogenase, which facilitates fixation of atmospheric nitrogen. These bacteria can do without salts of ammonia or nitric acid. It has been recently shown that these genes can be transferred into the cells of bacteria of other types that can't fix molecular nitrogen. As a result, the corresponding cells acquire the genes of nitrogenase, and their chromosomal apparatus proves to be altered in a controlled way. Of course, this is a model experiment. Yet let us imagine that we have been able to incorporate the genes of nitrogenase into wheat, cotton, or potatoes. We shall get plants that can live without nitrogen fertilizers. That is, we shall have economized on an entire, vast branch of industry whose necessity shall have declined.

Let us take a problem somewhat simpler. We need to produce certain proteins continuously in order to repair the defects that arise in people in serious diseases, such as insulin. If we stopped making insulin, diabetics numbered in the millions would die in several days. Insulin is currently extracted from the pancreases of cattle. This is a small protein whose gene is relatively easy to synthesize. Let us assume that we have incorporated such a gene into the chromosome of some microorganism (this is a quite practical problem). We

shall get a producer of the protein that we need, with which we can deal much more simply than with material from animal cells.

Finally, another possibility that still seems but a fantasy, but in principle can be transformed into reality is to introduce into the organism of people who are suffering from hereditary diseases genes that supplement the deficit of necessary enzymes that have been liquidated by a bad mutation that has destroyed the functional integrity of a certain gene. Again, if people solve the problem of introducing exogenous information into the cells of higher organisms, such a repair of the genome of human cells is not ruled out. We already know that certain viruses transfer genetic information from some cells of an organism to others—this is the so-called transduction. It is sometimes possible to transfer genetic information into cells by using purified DNA—this is the so-called transformation. Perhaps there are real possibilities here for active interference in heredity, that is, for gene engineering. The future will show.

The third problem that has become very topical in recent years is the viral origin of malignant tumors. It was shown long ago with the phage-bacterium model that a virus has two modes of existence: vegetative, when parasitizing the cell of a host, and latent, when it has vanished from the cell, but has implanted its chromosome into that of the host cell. Here the phage has been transformed into a prophage, or a virus into a provirus. Many properties of a cell change profoundly when it acquires this stock of new genes introduced by the parasite. One of the sharpest manifestations is the malignant transformation of cells. More and more observations are now accumulating that indicate that malignant neoplasms in man have the same source. The study of viruses, of the different forms of their interaction with cells, and methods of combating them are all problems of vast practical importance for human society. These problems are at the center of attention of modern molecular biology.

I might continue further and mention the importance of elucidating the details of protein synthesis (of which we yet know only the general features), of elucidating the structure and function of the protein-synthesizing machine (the so-called ribosomes), and the importance of the problem of automatic regulation of protein synthesis and the study of the details of this process, but I shall restrict the discussion to the examples given, which show how much modern molecular biology is a living, interesting subject.

Let us now proceed to the unsolved, new, very fundamental problems that have become the order of the day. It is yet unclear how to approach their solution, and serious advances have not yet been made. As it were, this is a scientific virgin soil that we have just begun to plow.

As the first of these problems, I mention morphogenesis, or the formation of structural elements, the so-called cellular membranes, organelles, and entire cells from biological molecules (proteins, nucleic acids, lipids, and carbohydrates). Molecular biologists have often been reproached for reductionism, i.e., for trying to reproduce vital processes in molecular solutions, for reducing vital phenomena to the reactions of molecules. Biologists counterpose reductionism with integratism, i.e., the self-sufficient importance of cellular and subcellular structures. The reproach for reductionism is thoroughly unjustified. No right-thinking person can deny that biological processes occur mainly, not in solutions, but in membranes and various structural entities: ribosomes, mitochondria, nuclei, etc. One of the founders of modern molecular biology, Jacob, in his recent book La Logique du Vivant, has introduced the special concept of the "integron."[2] By this he means a certain level of organization of matter at which it becomes possible to fulfill more and more complicated and refined functions. An individual protein molecule is the lowest integron. Beyond this are the numerous proteins, nucleic acids, and lipids combined in the structure of a membrane. This is the next integron in order of complexity. It solves a number of problems: it combines together many stages of enzymatic reactions to create a conveyer or automatic assembly line for synthesizing certain substances: proteins, fatty acids, or for gradually oxidizing them in stages (in the mitochondria). Further, the integrons of higher order are the cell, the tissue, and the organism.

Many problems immediately arise. What is the structure of membranes and cellular organelles? How do they perform their functions? How are they produced as the cell synthesizes their chemical components, i.e., the substances of which they consist? This is the problem of morphogenesis, the formation of the morphological elements of the cell, which are sometimes visible in the ordinary microscope (nuclei, mitochondria), and in any case, in the electron microscope (ribosomes, external envelopes of the cell). Physics has now "rolled up its sleeves" to solve these problems.

Very good studies have been carried out in recent years on the structure of the neuron membrane by x-ray diffraction. The resolution is as yet not too good, 10 Å, but there is considerable information.[3] One can see how the different classes of substances are packed within the membrane. In particular, the layer of lipid acts as a sort of insulating layer. Moreover, special substances have been found with a very interesting molecular structure. Their moelecules are large rings resembling bagels. These substances form the so-called channel complexes with sodium or potassium ions. The degree of complex formation of the ions with these peculiar molecules, which are called ionophors, depends on the radii of the ions. The ionophors are dissolved in the lipid film. Hence we get the selective permeability of membranes. While passing potassium at certain points, they are impermeable for sodium. Other ionophors bring about the permeation of sodium ions.

Along with passive transfer by diffusion, one observes the so-called active transport against a concentration gradient. Naturally, energy is spent in active transport, since it is the reverse of diffusion. The energy comes from oxidative reactions, i.e., respiration. Oxidation in living nature occurs in various membranes, in particular and most of all in special bodies, the mitochondria. The reactions involve participation of tens of proteins, or enzymes. The substrate to be oxidized, e.g., a sugar molecule, undergoes stepwise changes until it has ultimately been converted into carbon dioxide and water. Electrons are continually transported through the membrane in these reactions.[4] The electrons pass in a relay from protein to protein, since the enzymes con-

tain metal ions of variable valency, iron and copper, or special organic molecules that can be oxidized by electron transfer. As a result, the ordered organization of the catalytically active proteins in the membrane gives rise during oxidation to an electron current that charges the membrane to potential differences of the order of 0.1—0.2 V. With its small thickness, this can give rise to fields of the order of $(1-2) \times 10^5$ V/cm. Moreover, a transport of electronic current by a relay mechanism involving change of valency of neighboring ions is known in solid state physics in certain ferrites. The creation of an electric field in the membrane makes the cations move in one direction, and the anions in the opposite direction. However, the lipid layers insulate well, and only the presence of special ionophors creates channels for the movement of potassium, sodium, calcium, and other ions.

The electric fields in the membrane are associated with one of the most remarkable phenomena of biology: excitability. If the potential difference across a membrane, which amounts to 100—150 mV, is reduced at some point by a factor of 4—5, i.e., the so-called local depolarization occurs, whether by action of external potential differences or certain chemical agents (the so-called mediators). Then conduction arises in adjacent regions of the membrane. Consequently, a local depolarization current arises. Here the field across the membrane continues to decline, and its more remote regions become conductive.

Owing to these remarkable electrical properties, an electrical signal arises, or current pulse, which runs along the membrane without attenuation.[5] In the cells of the nervous system, or neurons, these electrical peaks, which have a temporal width of the order of milliseconds, are the ground material for manifestation of nervous and psychic activity. Electrophysiology is based on recording and trying to disentangle these signals, the so-called "spikes". However, they are not at all a privilege of neurons alone. Oen can easily observe propagating electrical signals even in plant cells. Most likely, they are a general manifestation of membrane functions, but the evolution of living nature has used them to create the nervous apparatus that has arisen in multicellular animals.

Nervous signals propagate with very characteristic velocities from 10 to 100 m/sec, mainly depending on the dimensions of the axon, i.e., the long cable formed by the nerve cell. These velocities were measured even by Helmholtz a hundred years ago. Now they can be calculated with sufficient accuracy.

Hodgkin and Huxley have created a phenomenological theory of the spikes. By measuring the electrical characteristics of the axon membranes by applying constant potential differences to them and substituting the measured data into the ordinary telegraph equation of Kelvin, they could correctly predict the shape and velocity of propagation of the signal. But what is the molecular nature of these properties of membranes that serve as the source for generating spikes?

It has been shown that a wave of perturbation of optical properties (birefringence, light scattering, and polarization of luminescence) runs along the membrane simultaneously with the electrical signal. While an individual membrane is very thin (50—70 Å), the specific optical effects are so large that one can measure them. Undoubtedly, this is the key to understanding the physical structure of the lipid "insulating" layers of a membrane. In nature, these liquid crystals, i.e., the lipid molecules, form domains of regular structure.

On the basis of modern domain concepts, we must not picture them as individual, bounded crystallites. According to the continuity theory of liquid crystals, adjacent molecules are oriented and packed in an ordered way, but with a certain perturbation that increases from molecule to molecule. Hence the order vanishes over the range of the correlation distance. Millions of molecules are packed in volumes of lipid having linear dimensions of the order of the correlation distance. Entire domains rotate in external fields, electric and magnetic. This is just why orientation in a magnetic field is possible in principle, as governed by the ratio $\mu H/kT$, where μ is the induced magnetic moment, and H is the magnetic field.

The lipids and other constituent parts of membranes are diamagnetic, but the domains are distinguished by diamagnetic anisotropy, While μ is a very small quantity for an individual molecule, and $\mu H/kT \sim 10^{-6}$, the situation changes sharply for a whole domain. Orientation of domains in electric fields is the basis of the remarkable electric properties of membranes that give rise to spikes, as well as of the optical effects mentioned above.

Finally, an orientation of the domains in strong magnetic fields has been detected, and it was shown that this orientation catastrophically affects material transport through the membrane.[6]

The concept of a liquid-crystalline structure of the lipid layer in a membrane explains naturally its remarkable electric properties. In fact, we have already taken up the topic of how to picture the electric conductivity of the lipid film with respect to sodium and potassium ions. Special and different ionophors exist for the two ions. Unfortunately, we have not yet found these substances in natural membranes, but chemistry has obtained entire classes of synthetic model compounds that have similar properties (e.g., gramicidin and enniatin). It has been shown that the helical or planar molecules of these substances collect in hydrocarbon film into stacks, or the so-called sandwich complexes. Ions migrate through the channels within these "sandwiches" when the sandwich is oriented normal to the membrane. Here we come to the molecular explanation of spike formation.

A membrane is charged in its initial state of rest, since it is permeable only for potassium ions, and impermeable for anions. Hence it become polarized up to the diffusional Nernst potential. When application of an external voltage source depolarizes the membrane at some point, the potential difference at this point falls almost to zero, while the electric-field vector at adjacent points of the membrane rotates by 90°. Since the ionophors for potassium and sodium are assembled into sandwiches, or in other words, into liquid-crystalline domains, their behavior when the electric-field vector rotates will be determined by their electric anisotropy, i.e., by the structural details of the molecules. Conductivity for potassium exists in the original membrane, but that for sodium is practically zero. Hence, the domains of the potassium ionophor are oriented parallel to the membrane, and those of the sodium ionophor are perpendicular. When the electric field rotates by 90°,

the domains rotate along with it. The film becomes impermeable for potassium and conductive for sodium. This is just what one actually observes. The sodium current will be in the opposite direction to the potassium current, and it will depolarize the membrane at the next point. The potential difference there will fall to zero, and this state will propagate along the membrane with a velocity that is given correctly by solving the Kelvin equation. This is how we can picture the origin of a spike.

Perhaps the most important function of membranes is their direct participation in morphogenesis, i.e., in production of new membranes. As I have stated, the problem of supermolecular structures and their genesis is one of the most exciting ones. The simplest structures are formed by self-assembly from proteins and nucleic acids at favorable values of the pH and the ionic strength. This was first shown with tobacco mosaic virus by Fraenkel-Conrat in 1955.[7] Although its structure is the most elementary: one RNA chain and 2130 identical protein subunits (Fig. 5), yet the possibility of assembling active virions in a test tube then seemed fantastic. Then the small bacteriophage MS2 was assembled from two types of proteins and one RNA molecule. Finally the situation came to the self-assembly of such a complex structure as T4 phage, which consists of tens of proteins (Fig. 6).

Interesting features were elucidated here. Self-assembly occurs in stages: heads, tails, and fibers are produced. Then they adhere to one another when special hydrolytic enzymes cleave protective groups on the end protein molecules. Here the structure is built also by self-assembly, but by a certain fixed program with distinct time stages.

The next step in complexity was the assembly of the subunits of ribosomes (Fig. 7). The small subunit of molecular weight 900,000 consists of 21 different proteins and one RNA molecule. It could be assembled in one stage by mixing all the proteins and the RNA in a test tube. The large subunit (molecular weight 1,800,000) consists of 34 different proteins and two types of RNA. It could also be built by self-assembly, but with curious variations. It turned out that the presence of complete small subunits in the solution greatly accelerates the assembly of large subunits, although the individual

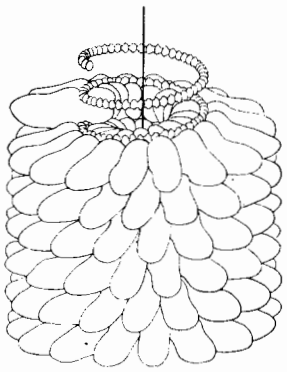

FIG. 5

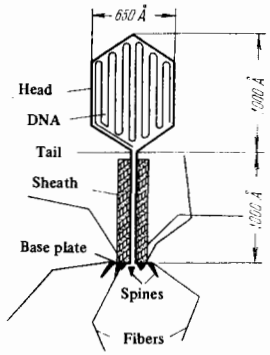

FIG. 6

FIG. 5. Model of tobacco mosaic virus. The protein particles have been removed at the top, and the RNA helix has been uncovered. (The model is built from X-ray structural data.)

FIG. 6. Diagram of the structure of T4 bacteriophage (based on electron-microscopic data).

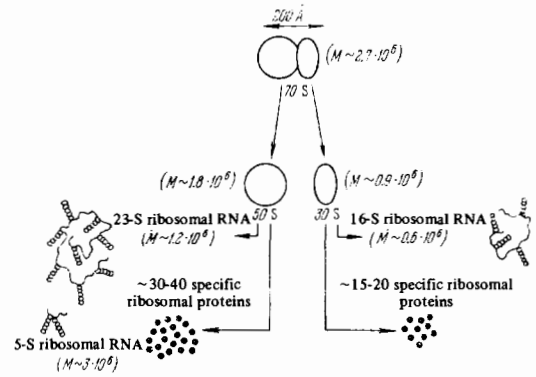

FIG. 7. Diagram of the disassembly and reassembly of ribosomes from three types of RNA and about 50 types of proteins.

protein particles of the small subunit in themselves have no effect on the process of assembly of the large subunit. Evidently the key thing is the completed surface of the small particle, with the arrangement on it of the different protein globules, which give rise to a force field near the surface that organizes the assembly of the second complementary particle.

If we seek simple physical analogies, then we might recall crystallization centers, which can be non-homologous to the liquid being crystallized. Thus, ice crystals grow on silver iodide centers because the field at the surface of a center is favorable for the appropriate arrangement of water molecules. An even closer analogy is that with the experiments in which one takes the surface of a monocrystalline metal, covers it will a thin amorphous film, and then evaporates onto it the original metal. Here the individual crystallites replicate the spatial orientation that had existed in the substrate. Information seems to be transmitted through the amorphous film on the surface structure of the metal, and it is reproduced afresh, i.e., duplicated.[8]

We have specially taken up this example since it is important for understanding morphogenesis in more complex cases. People originally thought that self-assembly exhausts all cases of morphogenesis, and that all the genetic information was actually contained in DNA in the form of data on the structure of all the proteins and nucleic acids. It has now become clear that this is not yet everything. The very architectonics of cellular structures, i.e., the various membranes, contains information on their structure, and transmits it to daughter cells in the processes of membrane assembly, similarly to the way that the small subunits of ribosomes aid the assembly of the large subunits. It has been shown that certain compact membranous structures multiply within the cell during the latter's growth. This is how mitochondria and the plastids of green plants behave. According to all data, they are self-reproducing templates.

Moreover, many experiments have been set up on certain protista and plants that show that a heredity of membranous structures exists in addition to nuclear heredity.[9] Thus, for example, the generally-known infusoria (the so-called paramecia or slipper animalcules) multiply both asexually and sexually. In sexual multiplication, two identical cells conjugate. That is, the link by means of a bridge, and exchange their small nuclei. Upon parting, the two individuals that had participated in the sexual process prove to be genetically identical. However, in the process of separation, one

of the cells can remove part of the other. A clear example might be the case in which one individual tears of the mouth structures of its partner and thus acquires two mouths. All the infusoria produced by division of a two-mouthed individual will have two mouths each. This aberration is conserved (Fig. 8). Two-mouthed infusoria can conjugate with normal ones. Both of the cells produced have identical nuclei, but after separation, the two-mouthed individual keeps this deformity. Hence the surface membrane of the cell is a self-reproducing structure. Its proteins are coded in the nucleus, but the information on its supermolecular structure of proteins and other components is contained in the membrane itself.

Let us give another characteristic example: the so-called biological isomerism.[10] A simple plant, the duckweed, has only three leaves, with somewhat differing shapes, which can form two mirror-image configurations, right- and left-handed, that are not mutually superposable (Fig. 9). The duckweed multiplies sexually, i.e., by seeds, and vegetatively, i.e., by budding. In vegetative multiplication, a new, small duckweed is formed in a special pocket in one of the leaves. A right-handed one is always formed by right-handed, and left-handed by left-handed. Yet when one sows a seed, one gets either isomer quite indifferently. The seeds of a given plant give right- and left-handed duckweeds with 50% probability. This means that the nucleus contains no information on right- or left-handedness. This circumstance is fortuitous and nonessential for the plant. However, this information is indelibly printed in the membrane of the leaf, and it is reproduced from generation to generation. Interestingly, one can get a discontinuity by injuring the duckweed with x-rays or chemical agents. Then one can get a left-handed descendant from a right-handed duckweed in the asexual, vegatative way as well. These examples exhibit hereditary information of a special sort, which is contained in the structure of membranes, in particular, the surface envelopes of the cell. We do not yet know just how this hereditary information is reproduced. Yet the vast importance of these phenomena is indubitable.

The second problem that I should mention is associated with the last one; this is the development and differentiation of the embryo, or ontogenesis.[9] A fertilized oocyte, or zygote, contains in its nucleus all the information on the different cells of many hundreds of types that comprise the tissues of the complex organism. The stages of development of the embryo

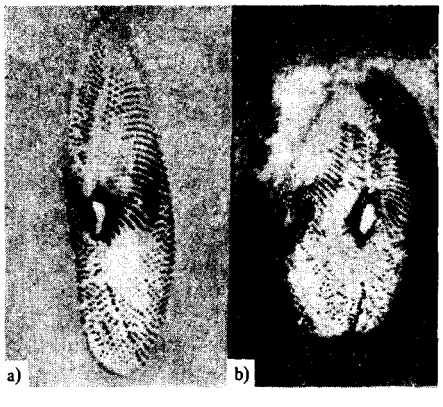

FIG. 8. Micrographs of (a) single-mouthed, and (b) double-mouthed paramecia.

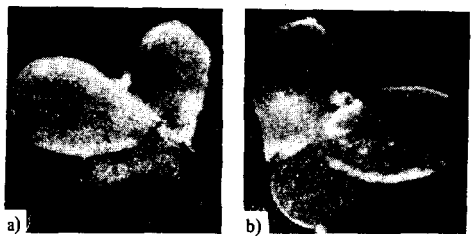

FIG. 9. Photographs of (a) left-handed, and (b) right-handed duckweed.

involve transition from more universal cells to ever more specialized ones—this is differentiation. The stages of differentiation arise suddenly after many cellular mitoses, and they are determined by special chemical agents, or hormones.

Evidently the principal problems in development are regulatory. How is a vast part of the genetic information in a differentiated cell suppressed, and only a few tenths of a percent of it realized? How does this global regulatory mechanism operate? Why is it irreversible, and why can dedifferentiation of somatic cells, i.e., bodily cells, occur in certain extreme circumstances? How far can one proceed along this path? The experiments of Stuart are already known; by making a dispersion of individual cells from the organs of a plant, e.g., a leaf, a stalk, or a root of the carrot, he was able to dedifferentiate them, make them universal, and then compel them to differentiate again on a suitably chosen medium in the presence of hormones to form a whole plant from each somatic cell.

Similar experiments are known on animals: transformation of cells of the intestinal epithelium of the frog into the semblance of embryonic cells by transplanting their nuclei into the cytoplasm of roe, and growing entire tadpoles from them. What determines such a reversal of differentiation? Why do viruses cause growth of tumors and simultaneously cause dedifferentiation when integrated into the chromosome? Here is a mass of problems, both structural and functional.

The packing of the DNA filaments in the chromosome is problem number one. Let us take for an example some human chromosome, e.g., number 13. It contains a DNA filament of diameter 20 Å and overall length 3.3 cm. Yet it is packed into a compact body of length 5.8 μm and diameter 0.7 μm. Evidently the Watson-Crick helix has been folded into a compact coil or spool. One asks how the genetic information is realized. How is the messenger RNA copied from the DNA of the chromosome? Microscopic examination of certain embryos permits us to draw conclusions on this process. In the microscope, examination of the chromosomes in the salivary-gland cells of fruit fly (drosophila) larvae shows that there are dense regions in the chromosomes and thinner ones. This is the so-called heterochromatin, in which the genetic information is sealed in and not expressed.

Along with this, there are disks with bulges, or the so-called puffs (Fig. 10). Their material, which is called euchromatin, is much looser in texture. In it the coil of DNA is partly uncoiled, and RNA synthesis proceeds vigorously on the DNA template. It has now been shown convincingly that each such disk contains one gene plus all the regulatory region of the chromosome pertinent to it. In all, one can detect something of the

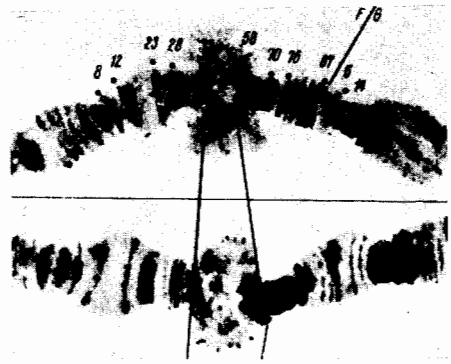

FIG. 10. Micrographs of chromosomes from the salivary gland of drosophila larva (puffs can be seen).

order of 5000 genes in drosophila by counting disks. In amphibian embryos also, the euchromatin regions, i.e., the functioning parts of the chromosome, are spread out and relaxed. The chromosomes in these objects have the shape of brushes for cleaning kerosene lamps. In the electron microscope, one can see in them the extended DNA loops. Here the Watson-Crick helix is uncovered, and can be copied. One asks what regulates the conversion of heterochromatin into euchromatin, and why the dense packing of the DNA filament gives way in places to a freer and looser structure. At present we can only guess about this.

Interesting experiments have recently been performed on models. Thus, they have taken the DNA of a virus, which forms a loose filament in solution, but a compact spool in the virion. In the presence of certain hydrophillic polymers dissolved in water (e.g., polyethylene glycol), the DNA of the virus itself begins to wind into a compact body.[11] The polymer dehydrates it, and then additional binding forces, apparently hydrogen bonds, begin to play a role, and the Watson-Crick double strand seems to crystallize into a superhelix. This process proved to be very sensitive to the ionic composition of the solution, e.g., to the concentration of sodium and potassium ions, One can maintain threshold conditions for coiling in the solution. Then one can fix intermediate structures in which the DNA filament is partly coiled and partly free.

All this somewhat recalls the situation in the chromosome. The nucleus contains a concentrated solution of hydrophilic polymers, or the so-called histones. Apparently the latter strongly affect the coiling and uncoiling of DNA. Perhaps one can compare their role with that of polyethylene glycol. But how is the uncoiling of DNA accomplished at precisely the needed points? How does nature make puffs at the regions of the chromosome where the embryonic cell needs them? We do not know. People suspect that there are special regulatory proteins of non-histone type that perform this function. Perhaps there is an extremely specific interaction here of these regulatory proteins directly with the DNA of the chromosome.

An estimate of the thermodynamic constants of this interaction gives unprecedented values of the dissociation constants of the order of 10^{-13} mole/liter and less. What molecular forces bring about such strong bonding (the decrease in free energy RT ln k is 16,000–20,000 cal/mole)? We are still groping in the dark, and must seek the laws of specific interaction of the regulatory proteins with DNA, just as Watson and Crick once sought the laws of interaction of DNA chains among themselves. It is as yet too early to draw a coherent picture of the events that might explain development and differentiation, but the avalanche of facts is growing, in particular and especially, facts gained by the methods and ideas of molecular biology.

I would like to turn now to the general problem of physical description of biological processes. Many physicists have called attention to the point that historism is foreign to physical laws. No physicists doubt that the fundamental laws of mechanics, e.g., the Schrödinger or Dirac equations, have been valid for all time, having undergone no historic development.

Yet living nature arose 10^9 years ago, and has passed through a vigorous evolution during which gigantic changes have occurred; from primitive one-celled beings, living nature has arrived at Homo sapiens. Hence, living nature is doubly historic, while the historic approach is foreign to physics. This has been pointed out, e.g., by Feynman. Yet this is a seeming contradiction. Actually, the equations of quantum mechanics are fully reversible, i.e., they are invariant with respect to time reversal. However, when one goes to statistics, i.e., to a large number of particles having randomly distributed initial conditions, the reversibility of time disappears. The modern theory of irreversible processes especially studies the problem of how, at what instant, and at what stage irreversibility arises. It turns out in the kinetic equations, whether they are the classical Boltzmann kinetic equation, or Pauli's kinetic equation in quantum statistics, or the more modern derivations of the kinetic equations of Van Hove and Prigogine, that loss of invariance with respect to time reversal always results from averaging over microscopic variables, by a so-called "coarse-structural" averaging over a "coarse-structural" distribution function, i.e., over regions of phase space large enough to average out the thermal fluctuations.[12] It is precisely from this averaging operation that irreversibility arises in the kinetic equations themselves, i.e., directional movement of the system toward an equilibrium state. The logical background consists in the fact that one applies an operation based on probability theory to the dynamic equations, which are absolutely reversible. Time acquires its sign in this procedure. Yet if one is studying a state of statistical equilibrium, then averaging over a region of phase space is equivalent to averaging over some interval of time. As the quasiergodic hypothesis of P. and T. Ehrenfest implies, this conclusion holds with great accuracy, and it permits one to conduct observations on one individually-chosen particle whose coordinates and momenta are averaged over a long enough interval of time to eliminate thermal fluctuations, although ultimately, the very application of statistics requires the existence of a large number of particles. The operation of obtaining the so-called "gross density" of points in phase space (i.e., averaging the density over a region of phase space that is very small with respect to its entire studied volume, but yet large enough to eliminate fluctuations) has a simple physical meaning. It corresponds to our way of formulating experiments and describing nature. Let us illustrate this with a simple example, We shall assume that we are taking measurements of a very weak current with a galvanometer. If the galvanometer is sensitive enough, and very free from inertia, i.e., it has a small intrinsic period, then it will continuously record thermal noise, i.e., fluctuations. Evidently,

our thermodynamic laws are inapplicable to the individual fluctuations, and the mechanical energy of the galvanometer arises from the thermal energy of the environment, i.e., in contradiction to the second law of thermodynamics. Such a situation is quite real. We recall the experiments of Prins and Zernike. However, one can take a different course under normal conditions, and record the current repeatedly with a condenser. It sums the thermal noise over a certain finite time period, i.e., it practically "annihilates" it. Consequently one can measure the current rid of thermal fluctuations. This is an averaging over a finite interval of time. As a result, we get rid of the fluctuations and study the process averaged over the entire statistical system.

All macroscopic quantities are precisely this type of indices. If one will, such a way of describing and perceiving nature stems from the fact that the observer himself is a macroscopic object consisting of a large number of molecules. It is precisely in such a description and study of nature by macroscopic indices that time-directionality arises, i.e., irreversibility of motion. Hence history is not at all foreign to physics when we are treating macroscopic processes. Moreover, evolution is not at all an exclusive privilege of biology. Our universe undergoes directional evolution, and the Earth evolves. Biological evolution is a detail of geological evolution, and is closely associated with it, since life must continually adapt to the varying conditions of the Earth.

One may ask what plays the role of the thermal fluctuations, or noise, in biology. Let us first consider unicellular organisms, e.g., bacteria. The fundamental task that a cell performs is reduplication, or division to form two daughter cells. The basis of this process is the autoreplication of DNA, i.e., the fundamental genetic material that the chromosomes are made of, and in which all the information on the proteins and nucleic acids is coded. The process of autoreplication, or literal copying, of the chromosome is based on simple physical principles. DNA is a two-stranded polymer chain. The two chains are not identical, but complementary. That is, they supplement one another.

Autoreplication of DNA follows the so-called semiconservative mechanism. The two DNA strands separate, and a complementary chain is synthesized on each of them as on a template, in line with the Watson-Crick principle. This is the situation in the ideal case, and it is confirmed now by thousands of varied experiments. However, thermal fluctuations, or noise, exist in the autoreplication of DNA. They consist in the fact that there is a finite probability of erroneous, non-complementary substitution of a chain link in which the hydrogen bonds can't be formed as assumed. Such a fluctuation will have a large additional energy of the order of 15,000 cal/mole, and it will not be observed often, but will follow the Boltzmann law: $e^{-U/kT}$. Undoubtedly, however, false, erroneous links in the DNA chain will arise. We note that errors will arise in both cells, mother and daughter, owing to the semiconservative mechanism.

The errors of autoreplication of DNA that arise from thermal fluctuations are the genetic noise. Their consequences are erroneous, altered enzyme molecules. In other words, this genetic noise is the mechanism of the so-called spontaneous mutations. The mutations are harmful in the vast majority of cases. That is, the altered enzymes perform their functions more poorly than the so-called wild-type (unaltered) enzymes. Only very rarely are mutations favorable and are established by natural selection. This is just why the process of evolution of species has taken such a long time: 10^9 years.

Unlike the fluctuations in Brownian movement, genetic noise does not dissipate, but remains in the given individual and accumulates in time. It disappears if one considers the entire statistical ensemble as a whole, i.e., the entire population of cells, Unfavorable mutations render the organisms less viable, and they gradually die out, being diluted by the "wild-type."

The irreversibility and directionality of processes in biology is quite evident from the life of each separate individual. We firmly know that each organism is born, lives, and dies, and it is impossible to turn this process backwards. This course of things is elucidated with a unicellular organism. For instance, a bacterial cell continually replicates itself and divides, and this constitutes its life. Here genetic noise must necessarily accumulate in it. We determine from the known probability of spontaneous mutations in bacteria that the error in autoreplication of DNA is 10^{-9} per link of the chain. However, the DNA in the cell contains something of the order of 5×10^6 links. If we consider that a bacterium divides once per hour, we can convince ourselves that, on the average, genetic noise will have already arisen in a bacterial cell in ten days, and it will persist. Over several months, the number of such errors will be expressed in the tens. Thus a corresponding number of defective enzymes will arise in the cell, and it will conduct its metabolism more poorly. This will be aging on the level of a unicellular organism. Irreproachable data are now accumulating that confirm the conception of aging of a cell as the accumulation of genetic noise, or spontaneous mutations.[13]

We may ask how to explain the aging of a complex, differentiated (in particular, human) organism. Undoubtedly, the fundamental basis is the same as in aging of unicellular organisms. Yet a complex organism is a coordinated system, and like every complicated device, it has its weak links that fall into decay first, and which destroy the entire mechanism. We do not yet exactly know what this weak link is in man. Certain physiologists think that it is the endocrine glands. However, the founder of modern immunology Burnet thinks that the reason for aging is exhaustion of the resources of immunological protection of the organism against infective diseases, i.e., aging and exhaustion of the lymphatic cells. Each such idea leads to an orderly conception, but one must spend much work to prove or reject it. This is as yet a task for the future. In any case, we see that the irreversibility of the life of a separate individual is based on statistics and thermal noise, just as irreversibility in thermodynamics is.

Upon proceeding to the volution of living beings as a statistical ensemble, we again encounter spontaneous mutations as the only cause of development, i.e., of the gradual, irreversible change in the system. In principle, we can describe the phenomena of spontaneous mutations and selection by using kinetic equations, as is done for irreversible processes in physics. These equations (those of the so-called population genetics) are well known, and they have repeatedly been studied. As a

whole, we see that the phenomena of biological evolution can be treated from the physical standpoint no more poorly than those of geological or astrophysical evolution.

Some curious additional problems arise when we go to the third problem, which I would like to mention: the problem of neurobiology and the code of the nervous system in man. Currently, owing to the study mainly of primitive animals having a very limited number of nerve ganglia, we have some fundamental conceptions on the operation of nerve cells.[14] First, it has been found that electrical impulses are generated in neurons by the action of chemical mediators, and they propagate without decay, owing to the energy stored in the axon membrane, which is a sort of cable in which the neuron ends. The electrical impulses follow one another at a certain frequency that describes the intensity of excitation. On the other hand, the amplitudes of the signals are attenuated in a certain way, and entire series of electrical signals having opposite phases are summed in special analyzer or integrator neurons. When different neurons are excited simultaneously, synaptic connections arise between them, i.e., electric contacts that serve as a model for conditioned reflexes and memory. Although we cannot yet describe exactly the entire machinery of coding and information analysis by cells, individual elements have already been explained: the mechanism of generation of an individual signal having a positive or negative (inhibiting) phase has already been elucidated, the nature of the frequency modulation of the signals is also understood, the analytical operation of neurons has been elucidated in principle, but not in detail, while the material nature of memory and reflexes is as yet a topic for theoretical speculations.

Yet the groundwork of the subject has already been laid. And here we cannot but touch upon two opposite approaches to these problems, two extreme and false viewpoints. One consists in the idea that the nervous system cannot be known because we are compelled in working with it to change its state so substantially that it thus comes to differ from the initially studied object. Viewpoints have been expressed that recall the early formulations of the Heisenberg principle. In 1937, Bohr held such an opinion.[15] This is what he wrote in his well-known article Biology and Atomic Physics: "First of all, we must clearly picture that every design of an experiment that would permit us to study the behavior of the atoms that constitute a living organism in as great detail as we can do with single atoms in the fundamental experiments of atomic physics rules out the possibility of keeping the organism alive. The continual material exchange that is inseparable from life makes it impossible even to approach the organism as an exactly defined system of material particles resembling the systems that are treated in every description of the ordinary physical and chemical properties of matter. Actually we are compelled to accept that biological laws proper represent laws of nature that supplement those suitable for explaining the properties of inanimate objects. Here there is an analogy with the relationship of complementarity between the properties of stability of the atoms themselves and the behavior of their constituent particles that allows a description on the basis of the coneept of localization in space and time. "And further, especially on the study of psychology:" The impossibility in a psychological experiment of distinguishing between the phenomena themselves and their conscious perception evidently demands a rejection of simple causal description in the image of classical physics; and the fact that one uses in psychological analysis the words "thoughts" and "sensations" insistently recalls the complementarity that one finds in atomic physics." We see that Bohr, however strangely, emerged as a vitalist. Indeed, he got over this vagary, and in 1959 in the article Quantum Physics and Biology, now relying on the well-known advances in molecular biology, he wrote: "Thus we have no reason to expect any internal restriction of the applicability of elementary physical and chemical concepts for analyzing biological phenomena." Hence Bohr had "cured himself" of his earlier errors. However, the teleological, vitalistic view of things, in particular the nervous system, is yet inherent in a very large group of biologists, and it is the source of many errors.

We do not consider it now necessary to combat these views. Evidently, the materialistic view of nature assumes it to be knowable on all levels, i.e., one can study the physical and chemical processes that are the material mechanism of psychological phenomena.

We should take up a second vulgar viewpoint that is extremely widespread among people involved in cybernetics and automation. This viewpoint consists in the idea that the psychic life and intellect of man can somehow be fully modeled by an electrical system that generates electrical signals similar to those that propagate and are analyzed in the nervous system. That is, one can create an adequate model of a person. This idea goes back to Laplace and the deification of mechanics in the early 19th Century. Replacement of a person by a quite adequate machine then seemed fully possible. However, we now deal with these notions more skeptically. When we construct models of nervous impulses and electrical networks, we reject everything pertaining to the concepts of human personality. We know that the nervous system of a psychologically normal person gives standard answers only to questions dealing with simple reflection of the outside world in one's consciousness. In all situations, however slightly more complex, that require choice of solutions, the responses of two different persons can not only differ, but sometimes they can even be diametrically opposite. Here the innate and acquired variations of the nervous and psychological system have their effect: different tendencies and abilities, and different experience fixed in memory.

With the same given supply of external information and external stimuli, the results with two different persons prove to be extremely different. In the operation of the nervous system, this means that the genetic noise, i.e., the innate, individual differences in the structure of the neuron network, acquires a decisive importance and it determines the final result in a no lesser sense than the external information does. Hence it is hopeless to create a model of a thinking person. In such a machine, one can model certain elementary processes of generation of electrical signals, and of their summation and analysis, but one cannot create a model of a human personality, since this is the result of superposition of an enormous number of thermal fluctuations, or genetic noise, whose effect is only amplified to a great degree by the entire physiological machinery of the nervous system. Hence, the topic that it is now possible and necessary to take up is the study of the physio-

logical machinery. Here the methods of physics have unlimited applicability and effectiveness, but this is only a small part of the problem.

We shall briefly take up one problem that is often discussed, that of incomplete determinism in the behavior of the nervous system of each separate individual, or the so-called free will. This problem consists in the following. Let us picture the nervous system of an individual with all its innate features. Let us picture a certain supply of external information entering the system and posing a certain problem for which different solutions can exist. One asks whether the solution that the given individual adopts is unambiguous, or whether it can change from time to time, and can be treated only statistically, i.e., probabilistically. We shall begin with the fact that even the experimental aspect is unclear: is there freedom to adopt solutions or not, every solution being fully determined by the external information and the hereditary structure of the neurons? We do not yet know. However, there would be nothing remarkable if solutions were adopted probabilistically and admitted fluctuations.

The nervous system of man is a statistical ensemble of about 10^{10} neurons. Each transfer and analysis of external information occupies entire regions of the brain, perhaps tens of millions of cells. Here also, statistical fluctuations, or noise, exist. The existence of this noise is well known to electrophysiologists. It is manifested in the passage through the neuronal network of current pulses that aren't correlated with anything. Thermal fluctuations, i.e., Brownian movement, always lies ultimately at the basis of this noise. The fact that they are manifested in the macroscopic system that is the brain is not remarkable. Above we have treated the case of current fluctuations in a galvanometer. We can easily imagine a similar macroscopic instrument designed precisely for the recording of sufficiently large discharges. A fully macroscopic executive mechanism will operate with random thermal fluctuations. It is not hard to imagine such a situation in the neuronal network. Evidently, here the adoption of solutions will depend on random fluctuations which in physical nature are nothing other than thermal noise. Hence, the concept of free will fits into the general statistical approach to the nervous system.

When evaluating the field of neurobiology as a whole, we must acknowledge that very little in it is yet firmly established. Let us take even the most fundamental fact that the nervous signals are electrical impulses. If we will, this fact is the outcome of the first biophysical experiment, the discovery of the movement of the frog's legs in Galvani's experiment (in 1791). However, there is no direct proof yet of the idea that the electrical signals are the initial cause of everything, rather than one of the consequences. Without such a direct proof, we find ourselves in the position of a person who has measured a leakage current into the ground surrounding an electric cable, and begins to assert that this current constitutes the fundamental process and basic function of the cable. However, we yet take it on faith that the electrical impulse that propagates in neurons is the material expression of nervous activity. This is a very likely conclusion. We know the mechanism of origin of a unit impulse. We know how the potassium-sodium pump charges the membrane of the neuron; the experiments of Hodgkin and Huxley showed how the unit breakdown or discharge of the membrane happens, and the experiments of Keynes and Tasaki[16] have found that a perturbation of the optical properties runs along the membrane of the axon simultaneously with the electrical signal.

However, all of this information is yet very elementary. Further, we have the results of studying the nervous systems of primitive animals, e.g., mollusks and worms, for which the entire nervous system consists of a few tens or hundreds of neurons. The facts of frequency modulation in the nervous system have been studied with these primitive electrical networks, i.e., the transmission of the intensity of the exciting signal in terms of the frequency of the repeated current pulses, together with the fact of the attenuation of the amplitudes of signals by the transmitting neurons themselves and the summation of signals having opposite phases that arrive from exciting and inhibiting neurons. All of this has been established in general outline.

But further, when we go to man, who has 10^{10} neurons, the situation becomes infinitely more complicated. Man transmits through his nervous system and analyzes the colossal information that is expressed by human language. Pavlov called this the second signal system. Since the individual impulses are primitive and of a single type, information transfer requires large series of impulses and special coding. If thought actually amounts to electrical signals, then what is the code that transmits human language by means of a sequence of primitive millisecond impulses?

At present, experimenters have learned to implant very tiny electrodes (a micron thick) into individual neurons of the human brain or into small groups of neurons. The recording of encephalograms from such small regions of the brain is a very complicated pattern in which it is hard to grasp what is noise and what is useful signal. When one looks at the experimental data of modern electrophysiologists, one is reminded of the situation in spectroscopy before atomic physics, before Bohr. It is a mass of strange correlations, with no clarity, and almost no general conclusions. For many physicists (who were in their time pioneers of molecular biology), there is much that is attractive hidden in this field of science, precisely because it is scientific virgin soil.

We can list some of those who have become interested in the problems of neurobiology. Brenner is now concerned with studying the electrical networks of neurons in primitive organisms. Benzer is trying to study the nervous system of drosophila with the aid of genetics. He has obtained a mass of curious mutants of the fly that imitate many of the psychological disorders of man, even as to fly-epileptics, fly-schizophrenics, and fly-homosexuals. Nirenberg is working with tissue cultures of nerve cells, and trying to understand how new synapses arise between cells, which might be the material mechanism of memory. All of the cited scientists are first-class biophysicists, who have been the authors of eminent discoveries in molecular biology. It is hard to say whether their undertakings will make any sense. They themselves are far from convinced of it. Nobody knows where to seek the solutions of the problems of the nervous system and the nervous code. When the trail has been blazed, thousands of people will crowd in, but today nobody can say with assurance how one should solve the problems. Yet no one doubts that these problems have a solution, and will be solved in the foreseeable future.

I would like to end the article with the words of Einstein, which one can apply to molecular biology more readily than to any other field: "The eternal mystery of Nature is its understandability."

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