The essence of biological evolution

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The current state of the theory of biological evolution is reviewed. Evolution is compared with the cosmological processes of structure formation. Both occur in dissipative systems and are governed by export of entropy. The objections to Darwin's theory are discussed and rejected. A sufficient material for evolution is indicated, as determined by the vast supply of variability of organisms. The reasons for this variability are described. The problems of speciation are discussed and its similarity to phase transitions is demonstrated. The phenomena of punctuated equilibrium and phyletic gradualism are described and examples of both are given. Special attention is paid to directional evolution. The views of L. S. Berg are examined in detail. Directionality is governed by natural selection, and also by the type of organism that has evolved and its possible variations. The link between individual and evolutionary development is studied. Wolpert's theory of positional information is presented and the concept of the model theory of morphogenesis is outlined. It is shown that a number of traits of organisms may have no adaptive value. The evolution of the visual organ is described. The molecular foundations of evolution and the neutralist theory, according to which the evolution of proteins and nucleic acids occurs to a considerable extent independently of natural selection, are studied in detail. Arguments in favor of this theory are presented and its physical meaning disclosed, which reduces to degeneracy in the correspondence between the primary structure of a protein and its biologic function. The results are presented of current studies that indicate the inconstancy of genomes, with various pathways of altering their structure and regulation. Various aspects of applications of information theory to problems of evolution are examined in detail. The evolutionary significance of the value of information, as defined as its nonredundancy, or irreplaceability, is stressed. The connection between the value of information and its complexity is studied. The value of information increases in the course of evolution. In conclusion, the sufficiency of material and time for evolution and the correctness of Darwin's theory are noted. Current problems of evolutionary theory are pointed out.

TABLE OF CONTENTS

This is an article about biology, written by a physicist for physicists. Its topic is to present the current state of evolutionary theory and to dispel some misunderstandings that arise at a secondary school level of acquaintance with biological evolution. Only to a small degree will we deal with physicomathematical models of evolutionary processes, although very rich results (see Ref. 1) have now been obtained in this field. In contrast, we have presented the data of biology and biophysics as fully as possible.

Of course, this article claims no complete coverage of such a vast theme. We have undertaken only an attempt to reveal the fundamental tenets of the theory and to point out its principal problems, which are yet far from solution.

An important place is occupied in modern physics by the study of open systems far from equilibrium. In such—dissipative—systems one observes events essentially different from those intrinsic to equilibrium. Spontaneous onset of space and time ordering can occur in an initially disordered system, owing to increase in fluctuations up to a macroscopic level. Living systems, starting with the cell and ending with the biosphere as a whole, are dissipative systems. Correspondingly, the most important problems of theoretical biology, the problems of development, prove to be very topical for modern physics.

1. INTRODUCTION

We know from childhood that living nature has developed by evolution, and that, as Darwin showed, evolution occurs by natural selection, which results in the survival of the fittest. Inheritable variability is caused by mutations, which have a completely random character and arise rather rarely. Thus, the number of spontaneous mutations per cell per generation of bacteria is of the order of 10^{-8}. Since natural selection occurs among mutants, and we are accustomed to think that an evolutionary system realizes a sorting of them, some questions arise that physicists always address to biologists. How could there be enough time for creation by evolution of the whole variety of existing species with their fantastically complex organs and behavior? And associated with this is the question of the material for evolution. If mutations are so rare, then how large must populations be in order that these improbable events are still realized? Where could the needed number come from?

Another characteristic question that arises upon preliminary acquaintance with biological evolution is the question of the origin of various biological structures and traits. In physics we ask "why," i.e. "from what cause?" In biology one often asks the question "what for," i.e. 'for what purpose?", since one assumes an adaptive meaning for each trait. What for did Cro-Magnon man, who belonged to the same biological species as modern man, need such a perfect brain? What for did the giant fossil deer *Megaceros eurycerus* require a horn of weight 25 kg? But, of course, there is a "from what cause": why do the eyes of cephalopod mollusks resemble in many ways those of vertebrates, whereas the faceted eyes of insects have a different structure?

Evidently any meaningful questions arising from living nature have an evolutionary sense. A fundamental feature of a living organism is its historicity: it passes through the path of individual development and bears the memory of biological evolution.

The aim of this article consists primarily in trying to answer these questions. As has been shown in outstanding studies of the past decade,[1-3] we encounter no features in evolutionary phenomena that bar the possibility of physical treatment. Modern physics suffices for understanding evolution. Here we may require new concepts, but not new physical principles.

Without discussing the methodological problems, we emphasize that vitalistic concepts, which counterpose biology to physics (and chemistry), are not constructive. On the contrary, searches for the physical content of biological phenomena and laws have a pragmatic value. The warnings sometimes heard against "physicalism" and "reductionism" in biology are meaningless.[4] The term "reduction" in this context is pointless. The discussion is focussed on integral approaches to natural science, not on reducing biology to physics, but on deriving the deep-seated tenets of biology from physics (cf. Ref. 5).

The imagined contradiction between the increase in complexity in the course of biological evolution and the increase of entropy in the evolution of an isolated physical system is easily removed. In biology we are dealing with open systems far from equilibrium (cf. Refs. 1, 6, 7). However, stating this evident principles does not suffice at all for constructing theoretical biology.

The ideas of historicity, development, and evolution have never been foreign to physics. They are based on the concept of irreversibility. All physical manipulations and measurements are essentially irreversible. The history of the second law of thermodynamics, which marked the transition from technology to cosmology[8] is instructive ("the universe is threatened with heat death").

We must note the influence of Darwin's theory on physics. One of the two founders of statistical thermodynamics, Boltzmann, called the 19th century the century of Darwin. The fundamental problem that Boltzmann was engaged in solving consisted in the substantiation in mechanics of the evolution of a physical system. Evolutionary physics was being created alongside evolutionary biology.

In its further development, thermodynamics passed from studying equilibria and quasistatic processes to studying irreversible processes in open systems. At first linear processes occurring near equilibrium were studied, then nonlinear processes far from equilibrium (Onsager, Prigogine *et al.*; see Refs. 1, 6-10).

Biological evolution constitutes part of the evolution of the universe and the evolution of the solar system. Biological evolution is localized in an infinitesimally small part of cosmic space—on the Earth. We possess no data on the existence of life outside the Earth (cf. Ref. 11). In contrast, the duration of biological evolution in time is commensurate with the time of existence of the universe, estimated to be of the order of 2×10^{10} years.[12-14] Life on Earth arose about 3.9×10^9 years ago, as witnessed by the oldest fossilized imprints of bacteria and primitive algae-microbionts. The age of the Earth itself is estimated to be 4.5×10^9 years.

Thus biological evolution was preceded by the origin and evolution of galaxies, the origin of the solar system and the Earth, and chemical evolution. The monograph of Ebeling and Feistel[1] gives tables of evolutionary events in which time has been contracted by a factor of 2×10^{10}. That is, the time that has passed from the instant of the "big bang" to the present is represented by one year. We reproduce the combined Table I from Ref. 1.

What do the evolution of the universe, of the solar system and of the Earth, and biological evolution have in common? In all cases we are dealing with the creation of new information, whether it is galaxies and stars, planets and folded mountains or biological species. The new information arises as a result of memorizing of a random choice (Kastler[15]) tha occurs if the initial state in a multistationary system is unstable. The creation of new information has the character of a phase transition.

The similarity of cosmic and biological evolution is not limited to this. The appearance of inhomogeneities—stars and galaxies—owing to gravitational instability implies competition and natural selection. The gravitational inho-

TABLE I. Calendar with time contracted by a factor of 2×10^{10}.

New Year's	Big bang.
June	Origin of galaxies.
September	Origin of the solar system and formation of the planet Earth.
October	First living beings, oldest known sedimentary rocks and fossilized imprints of microorganisms.
November	Microbionts producing oxygen develop widely. Origin of sexual reproduction. Appearance of photosynthesizing plants, first cells containing nuclei (eukaryotes).
Beginning of December	Formation of an oxygen atmosphere, intense volcanic eruptions. Development of meiosis and sexual reproduction.
Mid-December	Development of heterotrophic unicellular and the first multicellular organisms. Origin of macroscopic life.
Dec. 20	Origin of invertebrates.
Dec. 21	First oceanic plankton, flourishing of trilobites.
Dec. 22	Ordovician period; first vertebrates (fishes).
Dec. 23	Silurian; sporophytic plants conquer dry land.
Dec. 24	Devonian; first insects. Animals conquer dry land, first amphibians, flying insects.
Dec. 25	Carboniferous period; first coniferous plants, first reptiles.
Dec. 26	Permian; first dinosaurs.
Dec. 27	Triassic; first mammals.
Dec. 28	Jurassic; first birds.
Dec. 29	Cretaceous period; first flowering plants, extinction of the dinosaurs.
Dec. 30	Tertiary period; first primates, flourishing of mammals, first hominids.
Dec. 31	
About 2.00.00 pm	Origin of Proconsul and Ramapithecus.
About 10.30.00 pm	First humans.
About 11.00.00 pm	Stone tools.
About 11.59.00 pm	Discovery of agriculture.
About 11.59.30 pm	First cities.
About 11.59.54 pm	Invention of writing.
About 11.59.56 pm	Bronze metallurgy.
About 11.59.57 pm	Iron metallurgy.
About 11.59.59 pm	Euclidean geometry, Archimedean physics.
Midnight	1 A. D.
Jan. 1 (New Year)	
About 12.00.01 am	Introduction of the zero and decimal notation.
About 12.00.02 am	The Renaissance and modern science.
About 12.00.03 am	The present.

mogeneities compete with one another in gaining condensed matter.

The evident and universal thermodynamic basis of structure formation in cosmic, prebiological, and biological evolution is "entropy export"—its release by an open system.[16]

2. THE THEORY OF EVOLUTION IN BIOLOGY

Darwin was not the first evolutionist. One must cite Lamarck among his precursors. This scientist started with evolutionist concepts and studied the capability of organisms for adaptation. At the same time, Lamarck was guided by the unconstructive idea of an inner tendency of organisms toward perfection and assumed a multitude of acts of spontaneous generation, and thought that acquired traits are inherited.[17] These views are false, and we shall return to the last of them again.

The contemporary evolutionist Mayr considers the following four postulates of Darwin to be most important[18]:

1. The world surrounding us is continually changing. Extinction of species and appearance of new ones takes place.

2. The evolutionary process is continuous and gradual, having no jumps.

The first postulate is unconditional, but matters are not so simple with the second.

3. Related species come from a common ancestor. This holds also for any higher taxons, up to phyla. Ultimately all multicellular organisms have come from unicellular ones.

4. Evolution has been effected by natural selection. A heritable variability exists that is appreciable in each generation. As a result of the struggle for existence, the organisms are selected that are best adapted to the conditions of the environment.

The latter postulate is especially important, since it represents the mechanism of evolution.

Darwin's theory aroused objections. The first of these is "Jenkin's nightmare." As Jenkin pointed out, new traits selected in evolution cannot become established, but must be lost in cross-breeding. Cross-breeding does not single out, but absorbs the "useful traits." This difficulty has been overcome only by contemporary evolutionary biology, which has combined Darwin's theory with genetics. Traits are not absorbed, since they are determined by discrete genes, whose behavior follows Mendel's laws.

The second objection is a tautology, allegedly embedded in Darwin's theory. Those most fitted to the conditions of the environment win in the struggle for existence. The criterion for being fit is the survival of the largest fraction of descendants. But victory in the competitive struggle precisely means survival. Consequently, the point is that the "survivors survive." However, actually, the theory of evolution operates with independent definitions of being fit. Let us take up the classic example of "industrial melanism" of a moth, the peppered moth.[19] In the industrial regions of England in the 19th century, a mutant form of the moth with dark wings gained an advantage in propagation owing to the darkening of the bark of the oaks. These mutants are less noticeable on the bark of the tree than the light forms, and less destroyed by birds. Thus, adaptation has a quite clear meaning.

Finally, a number of authors have thought, and do think that "Darwinism is not a testable scientific theory, but a metaphysical program of study—a possible basis for testable scientific theories" (K. Popper; see Ref. 20).

What should we consider the testing of a theory to be? Evidently, we cannot yet experimentally reproduce evolution in the laboratory. Moreover, even if we succeed in forcing some system to evolve *in vitro*—in a flask— in no way will it repeat the single path of evolution known to us. Performance of a computer experiment based on a mathematical model of evolution also faces difficulties not yet overcome (see Ref. 21).

But in this sense biology does not differ from cosmology. A test of cosmological theory consists in its self-consistency, in observable confirmations of the conclusions of the theory, in particular in the existence of remnant radiation. In just the same way the paleontological record (and the exis-

tence of remnant organisms), and many facts pertaining to the contemporary biosphere serve as a direct confirmation of evolutionary theory.

The universe and the biosphere each exist as a unique sample. However, this is no impediment to scientific study of them.

How does modern theory answer the questions posed at the beginning of this article?

First, concerning the material for evolution. Genetic studies have shown that natural populations possess an enormous reserve of variability. Darwin did not know this yet. Genetic variability has a preferentially latent character—it is determined by a high degree of heterozygosity[1] always present in a natural population. Thus, the mean degree of heterozygosity of invertebrates is 13.4%, for vertebrates it is 6.6%, including 6.7% for humans, and for eight species of plants 18%.[22] The percent of mutant forms, i.e., percent of gametes (sexual cells) containing mutant genes is very large: for the fruit fly Drosophila it reaches 25%. The variety of traits upon which natural selection works is not determined by the small probability of mutation, but by the variability, which is reckoned in percents and tens of percents.

Heterozygosity in diploid organisms, i.e., in organisms whose cells contain a double set of chromosomes, implies the presence in these cells simultaneously of two allelic genes, say, a dominant and a recessive one. In subsequent cross-breeding, the latent traits are manifested.

The biallelic nature of diploid organisms, which multiply sexually, allows the trial and testing of new alleles in the presence of the old ones that have already been tested.

The evolving system is not the individual organism, but the population, i.e., the set of organisms of one species that exist in similar conditions, occupying a definite ecological niche and a definite geographic range.

The essence of the matter consists in sexual reproduction. The genome—the set of genes—of each new individual amounts to a recombination of the parents' genomes. Recombination is the mechanism of selection of the gene combinations. There are no two identical individuals. Birth of an individual implies the creation of new information—memorization of a random selection, since no laws of nature prescribe the appearance of a descendant with precisely a given pair. The appearance of sexual reproduction implied a great acceleration of evolution. Moreover, phenomena of transfer of chromosomes, similar to sexual reproduction, have been found and studied even in bacteria.[23]

Thus the material for evolution is practically unbounded. However, quantitative estimates are difficult. Nevertheless it is evident that a selection of optimally adapted organisms may correspond to any changes in the properties of the environment.

Correspondingly the question arises of the pace of evolution and the intensity of selection. This question involves the problem of directionality and irreversibility of evolution, which we shall discuss below. Here we shall restrict the discussion only to some examples.

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[1] See the list, "Some Biological Terms" following the main text of this article.

Races of different species of insects resistant to the insecticide DDT have arisen before our eyes. These are not yet new species, but new traits defined by alteration of genes have been created.

Rapid changes arise in the artificial selection of plants and animals. Darwin paid much attention to these phenomena, understanding that they simulate evolution under natural conditions.[24,25] Graphic results were obtained by D. K. Belyaev (see Ref. 26), who studied domestication of foxes. The fox kits are selected by a behavioral trait—by their tendency to make contact with man, i.e., those that do not fear man and do not try to bite him. When such foxes are kept in enclosures, literally for several generations, individuals appear with traits absent in nature. Foxes appear with pendulous ears, with a bent tail, with a shortened muzzle, etc. Belyaev associates this with the function of the hormones responsible for the behavior of the animal. At the same time it is evident that the change in the conditions of life, which removes the protective, stabilizing role of natural selection, can lead to appearance of traits that would be eliminated under natural conditions as maladaptive.

One can understand the origin of many domestic animals, in particular dogs. It is considered established that all breeds of dogs, from the Great Dane to the lap dog, have come from the wolves. Primitive man killed the she-wolf and the wolf cubs that bit or hid in the corner. He took home the wolf cubs that accepted food from his hand—to his children for amusement. And then a directional selection took place.

At the same time, artificial selection demonstrates the great stability of a species. New races and breeds are obtained, but not species. All dogs belong to the very same species. Substantial changes in natural conditions do not occur often, and divergence—the spread in traits necessary for occupying new ecological niches—takes time. We have mentioned the preservative function of selection. Modern evolutionary science distinguishes stabilizing and dynamic forms of selection (see Ref. 27). In the former case, which has been studied in detail by I. I. Shmal'gauzen[28] selection eliminates traits that diverge appreciably from the average norm. Stabilizing selection impedes evolutionary change, since the average norm has an adaptive advantage. A change in conditions leads to the action of dynamic selection that shifts the average norm (Fig. 1[29]).

The action of stabilizing selection is the "Red Queen Effect" from Lewis Carroll's "Through the Looking Glass": one must make an effort to stay in the same place.

Undoubtedly, sharp changes in natural conditions considerably accelerate evolution under the action of dynamic selection.

In a number of cases the opponents of Darwin's theory acknowledged the existence of stabilizing selection, but rejected dynamic selection (see, e.g., the work of L. S. Berg[30]). It was asserted that, when combined with random mutations, selection cannot create anything new. Here the fact was not taken into account that sets of traits are determined not by individual genes, but by combinations of them. Sexual reproduction brings about the sorting of alleles that fix new complexes of traits. This is precisely why "selection consti-
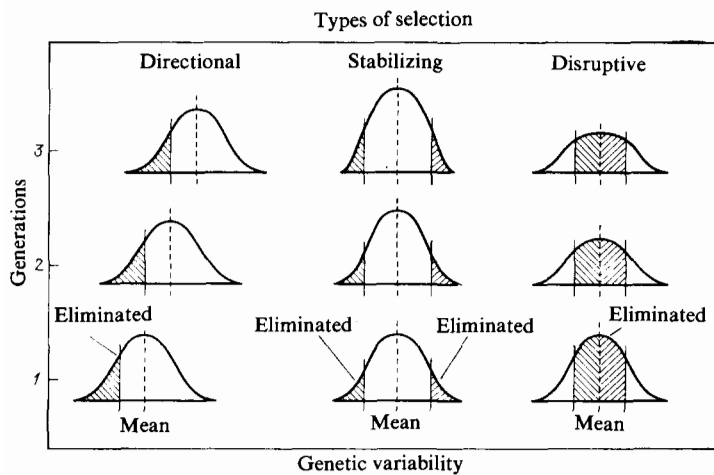
Types of selection

FIG. 1. Action of three different types of selection on the genetic variability in a population.[29] Disruptive selection is not discussed in the article; it favors conservation of the extreme types and elimination of the intermediate types.

tutes a mechanism capable of causing events that are improbable to the highest degree" (Ref. 29, p. 101).

3. SYSTEMATICS AND EVOLUTION

Living nature is characterized by the objectively existing hierarchy of the so-called taxons, or systematic units. These are the taxons: superkingdom (prokaryotes, i.e., unicellular organisms without nuclei—bacteria and cyanobacteria, and eukaryotes, with nuclei), kingdom (prokaryotes, plants, fungi, animals), subkingdom (for animals, unicellular and multicellular). Further, skipping the intermediate taxons, we come to the phylum (there are 23 phyla among animals) or division (plants have 22 divisions). The phylum is divided into classes (71 classes), the classes into orders, and then follow the family, genus, and species. Thus, humans belong to the kingdom of animals (Animalia), the subkingdom of multicellular animals (Metazoa), to the phylum of vertebrates (Vertebrata), the subphylum of craniates (Craniata), the class of mammals (Mammalia), the order of primates (Primates), the suborder of manlike higher apes (Anthropoidea), the superfamily of manlike primates (Hominoidea), the family of humans (Hominidae), the genus of humans (Homo), and the species of thinking humans (Homo sapiens).[31]

This classification reflects the genealogical link between the species. This is how living nature is organized. If there were no evolutionary links between the species, the existing systematics would be impossible. In this sense we should start the theory of evolution with Linnaeus—without his great discovery the theory of Darwin could not have been created.

The fundamental taxonomic category is the species. At present more than 1.5×10^6 discrete species have been described. Probably their actual number is three times as large. More than a million of the species are animals (among them about 850,000 species of insects), about 350,000 are plants, and about 40,000 are fungi. The number of species of prokaryotes is several thousand.[29] At the same time, according to paleontological estimates, the number of existing species amounts to no more than 0.1% of all that have ever lived— 99.9% of the species have died out.[32]

The species is a concept that is relatively exactly defined for organisms that multiply sexually. A species is a set of individuals resembling one another, having common ancestors, and breeding in nature only with one another. Crossbreeding with representatives of another species can result in offspring—hybrids (the mule is a hybrid of the donkey and the horse), but this progeny is sterile. The reason is that each species is characterized by a quite definite set of chromosomes—the karyotype. Two different karyotypes are incompatible, and in subsequent meioses, in the case of hybrids, cannot form gametes that yield a viable zygote, or fertilized oocyte. On the microscopic level the fundamental species classification is the karyotype.

Species are highly discrete, precisely because most of them have become extinct and intermediate forms are practically lacking. This greatly facilitates the systematics.[33]

The formation of species results from accumulation of changes of genotypes. The changes in abundances of alleles are determined by mutational processes, by the flux of genes, i.e., changes in the composition of the population owing to migration into it of new individuals, by natural selection, and gene drift, i.e., random variations in the abundances of alleles and genotypes (Ref. 29, Chaps. 4 and 13). New species arise from the action of isolating mechanisms. Isolation can be spatial, geographic, ecological, when the separated populations occupy different ecological niches, or reproductive, consisting in the impossibility of generating fertile offspring (Ref. 29, Chap. 19).

S. S. Chetverikov (1905) showed that the populations of all living organisms are subject to fluctuational variations in number. He called these changes the "waves of life." They can be highly significant. This leads to changes in the frequencies of mutations and to changes in the geographic distribution of populations. Thus the "waves of life" play an appreciable role in speciation (see Ref. 27).

Despite the initial position of Darwin on the absence of jumps in evolution, the appearance of a new species have a jumpwise character. Shmal'gauzen wrote: "The transition of an organism from one type of adaptation to another is essentially a jumpwise process" (Ref. 28, p. 386).

Following Ref. 34, let us examine a simple model of

speciation. Let us assume that the population consists of diploid organisms. The original wild type is characterized by the allele A, and the mutant by allele B. The possible genotypes are AA, AB, and BB. They are characterized by different coefficients of adaptedness, respectively equal to w_1, w_2, and w_3. We define the quantity $\omega_i = f_i g_i$, where f_i is proportional to the number of surviving gametes, and g_i is proportional to the fertility. The dynamics of the frequency p of gene A (the frequency of gene B is $1-p$) is described by the equation[35]

$$\frac{dp}{dt} = p\,(1-p)\,\frac{(w_1-w_2)\,p+(w_2-w_3)\,(1-p)}{w_1 p^2+2w_2 p\,(1-p)+w_3\,(1-p)^2}$$

$$-\mu p+\nu\,(1-p). \tag{1}$$

Here μ is the frequency of forward mutations A $\to$ B per generation, and ν is the frequency of back-mutations B $\to$ A per generation. The time is measured by the number of generations. It is assumed in deriving (1) that μ, $\nu \ll 1$, and $w_1 - w_2$, $w_2 - w_3 \ll w_3$.

Let us rewrite Eq. (1) in the form

$$\frac{dp}{dt} = G^{-1}\,(p)\,(a_0-a_1 p-a_2 p^2-a_3 p^3). \tag{2}$$

Here we have

$$G(p) = w_1 p^2+2w_2 p(1-p)+w_3(1-p)^2 > 0,$$

$$a_0 = \nu w_1, \quad a_1 = \mu w_1 - \beta, \quad a_2 = \beta\,\frac{3q-1}{q},$$

$$a_3 = \beta\,\frac{1-2q}{q}, \quad \beta = w_2 - w_3.$$

The quantity q expresses the degree of dominance of allele A in the heterozygote AB. That is, we have

$$0 < q = \frac{w_2-w_3}{w_1-w_2} < 1. \tag{3}$$

We assume that $\beta \ll w_i$, $\nu \ll \mu$.

In the stationary state of the population we have $dp/dt = 0$, and

$$a_0 = \varphi\,(p) = a_1 p + a_2 p^2 + a_3 p^3. \tag{4}$$

A change in the conditions of existence of the population corresponds to a change in the parameters β, μ and ν on which the pace of evolution depends (Eq. (2)) and its final result—the stationary value of p according to Eq. (4). Figure 2 shows the diagram of the stationary states of p for different values of β in the case $q < 1/3$ ($a_2 < 0$, $a_3 > 0$) and $\beta < \mu w_i$ ($a_4 > 0$). The cubic equation (4) has three real positive roots
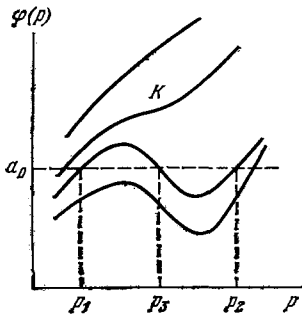
p_1, p_2, and p_3. They coincide at the critical point β_c, which can be easily found. Kinetic models described by equations of this type have previously been treated by Schlögl[36] (see also Refs. 6, 7, and 37). The diagram resembles the van der Waals curve. If we correlate a_0, a_1, and p respectively with the pressure P, the temperature RT, and the concentration $1/V$, Eq. (4) corresponds to the equation of state

$$P = \frac{RT}{V} - \frac{C_2}{V^2} + \frac{C_3}{V^3}, \tag{5}$$

which resembles the van der Waals equation in virial form. When $\beta < \beta_c$, we have three stationary values—the stable p_1 and p_2, and the unstable p_3. The stationary system can exist in two locally stable states that substantially differ in values of p—the frequency of genes. The transition between these states resembles a first-order phase transition. The transition, which we can treat as the formation of a new species, is caused by sufficiently large fluctuations of composition and number of the population.

Now let us assume that the population is spread continuously in its geographical area. The population dynamics is described by the equation for a distributed system including diffusion, i.e., migration of individuals:

$$\frac{\partial p}{\partial t} = \psi\,(p) + D\Delta p. \tag{6}$$

The diffusion coefficient is $D = \bar{r}^2/2$, where $\bar{r}$ is the mean distance to which individuals migrate in their lifetime, Δ is the Laplacian, and $\psi(p)$ is the right-hand side of Eq. (2). Diffusion does not break down the stability of spatially homogeneous stationary states—solutions for the point system (4). However, here a stable, spatially inhomogeneous distribution $p(\mathbf{r})$ can arise. Two spatially separate phases can arise, each of which corresponds to a stable state. According to (6), the condition for their stable coexistence is found by minimizing the functional

$$\Phi = \int d\mathbf{r}\,\mathscr{L}, \tag{7}$$

where $\mathscr{L}$ is the Lagrangian:

$$\mathscr{L}\,(p,\ \nabla p) = \frac{D}{2}\,(\nabla p)^2 - \int \psi\,(p)\,dp. \tag{8}$$

Minimization of Φ at constant total volume of the system when the volume of the transition layer is much smaller than the volume of each phase yields

$$\psi\,(p_1) = \psi\,(p_2) = 0, \quad \int_{p_1}^{p_2} \psi\,(p)\,dp = 0. \tag{9}$$

The first equality of (9) is the condition for stationarity of the solutions p_1 and p_2, and the latter is analogous to the Maxwell condition for a van der Waals gas.

The spatial stratification of a population is the first stage in the so-called allopatric pathway of speciation. In this case the new form arises and is established in a territory that it had not previously occupied. The further existence of the allopatric form leads, now secondarily, to accumulation in it of new traits and to biological isolation. The geographic separation of the population resembles the spatial stratification in a first-order phase transition.

The structure of a population evolving according to Eq. (1) can also undergo transitions resembling second-order

phase transitions if the stability of the stationary states with respect to small fluctuations is broken at certain bifunctional values of the parameters. Such a transition occurs when a_1 vanishes, i.e., when $\beta = \mu w_1$. When $\nu = 0$ $(a_0 = 0)$ at the point $\beta = \mu w_1$, the stationary p (a_1) relationship has a break characteristic of a second-order phase transition (Fig. 3). The quantities p, a_0, and $a_1 = \mu w_1 - \beta$ prove to be analogs of the magnetization, the magnetic field intensity and the deviation from the Curie point T_C—the quantity $(T - T_C)/T_C$ for a ferromagnet-paramagnet transition. Correspondingly one can show that a sharp rise occurs near the transition point in the relaxation time of the small fluctuations in the stable stationary state and in the responsiveness of the system to a variation of the parameters. In a distributed system,[36] with the added inclusion of random external agents, the bulk fluctuations and the correlation range of the fluctuations increase as the transition point is approached. The transition to the new organization via an unstable state occurs fluctuationally—all large volumes are occupied by correlated fluctuations that result from small external disturbances. In such situations the population acquires a lability that can lead to rapid progressive evolution, e.g., emerging into a new adaptive zone (aromorphosis, see below). Such a "disclosure of evolutionary reserves" occurs at a low selective elimination $(\mu = \beta /w_1)$. In evolution the stages of continuous development in a stable regime alternate with transition stages similar to phase transitions. The transitions are of nonequilibrium type. The modeling, theoretical study of evolution is the study of a dissipative system—a field that is commonly called synergetics.[38]

The results of this study coincide with the qualitative ideas of A. N. Severtsov.[39] Let us present his schema (Fig. 4): "At a certain stage of the evolutionary process in a given form of animals (A), traits of progressive character develop. That is, aromorphosis occurs . . . This rise in organization is indicated in the diagram by a certain rise in the line $(a_1 \ldots a_2)$ that symbolizes the course of evolution of the given group. Following this rise in organization, the given group begins to adapt to the different conditions . . . of the environment . . . , i.e., in other words, adaptations (b, b') to the different conditions of the environment occur. The given group, upon finding itself under different conditions, breaks down into a greater or smaller number of systematically subordinate groups . . . We can denote this period of the life of the descendants of our group as the period of idioadaptation."[39]

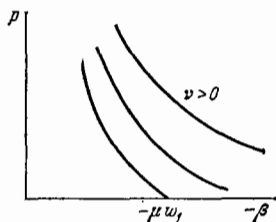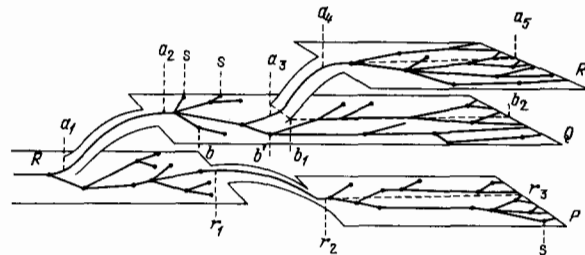The aromorphosis of Severtsov resembles a phase tran-

FIG. 4. Diagram of the evolutionary process according to Severtsov.[39]

sition. L. S. Berg wrote on the same theme (Ref. 30, p. 302): "The birth and death of individuals, species, and ideas is a catastrophic process. The appearance in the world of all these categories is preceded by a long, latent period of development that occurs on the basis of certain laws, and then a jump—saltus—suddenly occurs, expressed in their appearance in the world, propagation over the earth's surface, and winning of a "place in the sun." The process of transition of a gas to a liquid is a jumpwise change."

The comparison of speciation with the liquefaction of a gas is very remarkable. Reference 34 confirms Berg's idea.

Evidently the Darwinian divergence—origin of two or more species from a common ancestor—implies the growth of specialization and correspondingly a decrease in symmetry. Divergence resembles a phase transition.

One of the fundamental problems, far from solution, of the contemporary theory of evolution is the connection between microevolution and macroevolution. Microevolution is the evolutionary changes within a population, including speciation. Changes above the level of the species—establishment of higher taxons—are macroevolution. Do the mechanisms responsible for microevolution explain macroevolutionary events? As we see, the answer is negative: the accumulation of small changes still does not mean a phase transition.

In this sense even speciation differs from the microevolutionary accumulation of small changes. At the same time the transitions themselves can differ—the breaks between species can be larger or smaller. In some cases intermediate species are easily defined. In other cases intermediate species may not exist.

The paleontological chronicle is vast and is continually being enriched. But often gaps figure in it—the intermediate species are not discovered. Is this a consequence of the incompleteness of the chronicle, or are the jumps between the species so large that the intermediate species simply did not exist?

There are two fundamental models of speciation: the result of natural selection within an existing species and "genetic revolution." In the former case the term used is "phyletic gradualism." In the latter case it is "punctuated equilibrium."

Figure 5 shows a schematic diagram of speciation in the two cases (see Ref. 49, p. 284).

A detailed analysis of the genetic relationships on the molecular level for a number of species of contemporary fishes leads to the conclusion of phyletic gradualism in these cases.[40] Analogous results have been obtained in studying
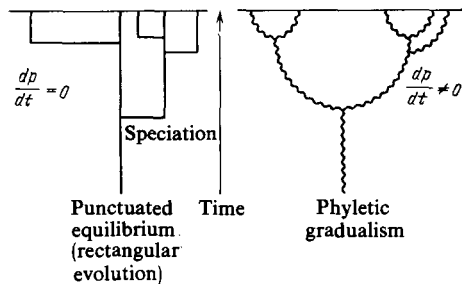

FIG. 3. A variation in the structure of a population similar to a second-order phase transition.[34]

FIG. 5. Diagram of gradual and rectangular evolution; rate of variations of the phenotype.[49]

the evolution of hominids over the past 4×10^6 years—in essence here all the intermediate forms have been found.[41] Yet the study of speciation in the genus *Drosophila* favors "punctuated equilibrium." A small, isolated population of an initially widespread and highly variable species undergoes large genetic changes owing to random loss of alleles, increased frequency of homozygotes (inbreeding), and resultant breakdown of the interacting complexes of genes and processes of development occurring under genetic control. The new isolates can move into previously unoccupied ecologic niches; consequently they can sharply increase in number.[42]

Thus both types of speciation can occur—with less sharp or with sharper transitions.

Species differ. É. Vrba proposed to distinguish "generalists" and "specialists" (see Ref. 43). "Specialists" are tolerant of similar species, since they occupy narrow, specialized ecological niches. Yet small changes in the environment can drive them from their niches. Thus the "specialists" easily die out or change. On the contrary, "generalists" occupy broader niches, they are more resistant, and less tolerant of similar species. Correspondingly their evolutionary changes occur more slowly. What we have stated is illustrated by the diagram in Fig. 6. An example is: 27 species of Alcelaphini have appeared in 6×10^6 years, and only 2–3 species of Aepycerotini (both belong to the family of antelopes).

Further discussion of these problems without elucidating the reasons for irreversibility and directionality of evolution is impossible. Any detailed modeling is also impossible. Above we have restricted the treatment only to a very simple model of the illustrative value.
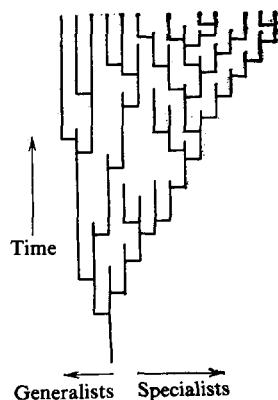

FIG. 6. Diagram of the evolution of "generalists" and "specialists."[43]

4. DIRECTIONALITY OF EVOLUTION

The above presentation implies that there has been sufficient material for evolution. It also follows that evolution can be fast. But is its speed sufficient for the origin of such a complex biosphere?

The starting material for evolution is mutations. They are completely random and not directed.

The directing factor is natural selection, which vectorizes the development of morphophysiological properties useful for the species (see, e.g., Ref. 27). However, it is not the sole directing factor.

We must from the outset reject the ideas of Lamarck on the inner tendency of organisms toward perfection and on the inheritance of acquired traits (IAT). The latter implies the transmission to the sexual cells of adequate information on events that have occurred in the somatic (nonsexual) cells of the adult organism. No one has ever sought the mechanisms of such a transmission, and it is impossible to imagine such a mechanism. A vast number of experiments has unequivocally rejected IAT; these concepts have already long lain outside science. IAT was the guiding idea of T. D. Lysenko. However amazing this may be, attempts are still being made to resuscitate IAT, but in the popular-science press. At the same time, an exhaustive critique of these views[45] has been published in the pages of the same journal. We remark parenthetically that Darwin did not deny IAT. However, this hypothesis is not essential for his fundamental idea of dynamic natural selection as illustrated in Fig. 1 on the left-hand side.

The concept of IAT was maintained longest of all in microbiology. The problem of transmission of adequate information to the sex cells is absent when we are speaking of bacteria. Hence the "habituation" of bacteria to an antibiotic, say the "habituation" of pneumococci to penicillin, has been treated as IAT, as an adaptation of the bacteria to the antibiotic. However, it has been shown by precise quantitative experiments that the question here is of mutations—penicillin acts as a selective factor. All the pneumococci perish with the exception of the mutants resistant to penicillin, which multiply without hindrance (Ref. 47; see Ref. 48, p. 87). IAT exists neither in eukaryotes nor in prokaryotes.

Darwin's theory has been counterposed not only by the ideas of Lamarck. The nomogenesis of L. S. Berg merits more attention today.[30]

Berg's study, which was published in 1922, is called "Nomogenesis or evolution on the basis of regularities." The fundamental idea consists in a primordial directionality of evolution—nomogenesis is counterposed to the Darwinian "tychogenesis"—evolution on the basis of chance. Berg thought that "progress in organization does not depend in the smallest degree on the struggle for existence, that Darwinism requires an infinite variability . . . We assert that the number of mutations is limited, and selection has nothing to select from" (Ref. 30, p. 112).

As we have seen, this tenet is false, but in 1922 modern genetics and the modern theory of evolution did not yet exist.

Berg asked the question (quite reasonable): how could

522   Sov. Phys. Usp. 27 (7), July 1984

M. V. Vol'kenshteĭn   522

the eye, the ear, and the brain arise by chance? In presenting a number of arguments favoring directed evolution, he arrived at the conclusion of the absence in nature of dynamic selection, and that selection can only be stabilizing.

In the light of present-day knowledge, the error of this concept is obvious, but Berg's argumentation and many of his ideas are of great significance—this major scientist was ahead of his time in many ways.

Even the best modern monographs and textbooks on evolution[19,27,29] hardly discuss directionality of evolution. Berg wrote:

"Darwin assumed that the variability of traits occurs in all directions . . . But we believe that the variation of traits is confined by certain boundaries." (Ref. 30, p. 158).

"Completely arbitrary forms from which selection is supposed to choose the most adapted ones do not arise. On the contrary—the organs are formed that must be formed in view of the constitution of the organism and the external conditions" (Ref. 30, p. 287).

"Selection must operate with a preexisting tendency, rather than with chaotic random traits that appear without any rules" (Ref. 30, p. 288).

Thus he stresses the dynamic, rather than the statistical nature of evolution. He notes the significance of convergence—the appearance in genetically remote genera of similar traits and similar directions of further development. "Similarity in the organization of two forms can be the result of coming from common ancestors, but it can be merely the consequence of a certain uniformity of the laws of nature" (Ref. 30, p. 287).

As we shall see, all these views are correct. However, certain conclusions that Berg drew from them are false. Directionality of evolution is not counterposed to dynamic natural selection; the existence of convergence in no way abolishes divergence in the result of natural selection. The denial of natural selection actually has no scientific basis. However, accusations of L. S. Berg of vitalism and idealism were not to any degree valid. Berg clearly formulated the views on the dependence of directed evolution on the physicochemical properties of proteins: "There are no miracles in the world: nature works exclusively with the laws of physics and chemistry" (Ref. 30, p. 113).

Modern theoretical biology assigns paramount significance to the second directive, vector factor of evolution—to the restrictions determined by the already constituted type of structure and nature of its changes in individual development. In other words, the connection between ontogenesis and phylogenesis—individual and evolutionary development— is of greatest significance. A summary of the modern views in this field is contained in the collected volume of Ref. 49; see also a brief resumé of it in Ref. 50.

Upon turning to these problems, we go from the organismic to the supercellular and cellular levels of organization. Further on we shall have to descend down to the molecules. Without this one cannot understand evolution.

The power of natural selection is limited by the type of structure of the organism and the dynamics of its ontogenesis. To understand what selection cannot do is no less impor-

tant than understanding what it can do. Why do all terrestrial vertebrates have four extremities? Why don't liver cells arise at the ends of the fingers? We can consider it established that the major types of cells of vertebrates have not changed in 500 million years. Nor have their properties changed—their capacity for mitotic division, programmed death, physical chemistry of intercellular contacts, chemotaxis, and capacity for mechanical deformation. The evolution of morphogenesis, i.e., structure formation in individual development, implies changes in the spatial and time utilization of the fundamental cellular mechanisms, but not a change in these mechanisms themselves. We can assert that the evolution of the cells of multicellular organisms does not contain so much that is new, but the distribution and intensification of the functions in individual cells fixes a new spatial structure and a new behavior in time.

Thus the restrictions that vectorize evolution are imposed by the properties of the cells themselves. In essence, macroevolution amounts to escapes from these restrictions.

Here we encounter the fundamental principle or organization of living nature. On all levels, starting with the molecular, a new combination occurs of a limited number of previously created elements—amino-acid residues of proteins and nucleotide residues of nucleic acids, cellular and intracellular membranes, types of cells and cellular mechanisms. Identical organizations are utilized for different purposes at all levels—the contractile protein actin acts in the muscle of a weight-lifter and in the tail of his spermatozoa, the lung of the amphibian arose from the swimming bladder of the fish. This fundamental rule on the whole explains the speed of evolution—the "assembly" of all possible structures takes place with identical parts.

As we know, one can divide individual development into quite definite stages. The transitions between them also have the character of phase transitions. The morphology of a given stage creates the "initial conditions" for the next. The given stage determines the restrictions on the development of the next. Thus, without formation of the primary cavity of an embryo in the blastula stage, differentiation of the types of cells could not arise and the next stage—the gastrula—could not be formed (see, e.g., Refs. 33, 51).

In this regard we should take up the problem of regeneration. Primitive organisms—sponges and hydras—regenerate themselves from separate pieces. Upon dispersion and subsequent mixing of their cells, these organisms are reconstructed—cells of a single type "recognize" one another. It would seem that regeneration offers advantages and actually implies a certain utilization of "spare parts of the machine." However, in the course of further evolution this capability is lost. Apparently there is an adaptive advantage in the suppression of regeneration involving a decreased frequency of malignant neoplasms. At the same time the loss of regeneration is the price for integrity of the organism, for the unity of its nervous system.

Biological technology proves to differ from industrial.

The conditions that arise in the course of ontogenetic development create new possibilities for cells—possibilities of interacting, carrying out morphogenesis, and differentiat-

ing. Thus controlled normal development is realized (see Ref. 52).

Specialization of cells arises already at the early stage of the cellular sphere—after five or six divisions. Evidently the cells lying inside the sphere exist under different conditions than those on its surface.

Metamorphosis occurs in a number of organisms: the larval stage substantially differs from the stage of the adult (say, the caterpillar and the butterfly). Evidently the larvae and the adult organism exist under completely different ecological conditions. The structure of the larva is the source of the positional information required for metamorphosis, which has the character of a phase transition.[53]

The concept of positional information (PI) was introduced by Wolpert (see Refs. 54 and 55).

According to Wolpert, the plan of development of the embryo is created by the sensing and interpretation of the PI by the cells. In embryos the cells are organized in space, initially recognizing where they lie, and then interpreting this information according to their genetic program. The differences in the structures of organisms are not determined by the cells as such, but by their relative spatial arrangement. About 200 types of cells exist in all vertebrates. All of the skeletal-muscular system of any animal is a spatial variation of a few cell types. Thus nonequivalent states of cells are essential. The number of such states can be larger than the number of types of cells.

The subsequent mathematical models of Gierer and Meinhardt (see Refs. 56 and 57), which rest on the classical study of Turing,[58] are related to the ideas of Wolpert (see also Refs. 1, 6, 7, 9, 10, and 59).

A space-time structure can arise in an autocatalytic dissipative system. As a model of such a system, we can treat the coupled chemical reactions

$$A \to X,$$
$$2X + Y \to 3X,$$
$$B + X \to D + Y,$$
$$X \to E.$$
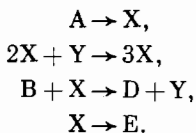
The overall reaction is $A + B \to D + E$. The second stage is the autocatalytic one.

The kinetic equations in terms of dimensionless variables have the form

$$\frac{dx}{d\tau} = a + x^2 y - bx - x,$$
$$\frac{dy}{d\tau} = -x^2 y + bx. \tag{10}$$

Such a point system can undergo autooscillations. When $b = a^2 + 1$, the singular point corresponding to the stationary state is the center. When $b > (a + 1)^2$, the singular points are unstable nodes, but the system approaches a limit cycle.

Turing was the first to treat a distributed, rather than point, dissipative system. Let us supplement the equations (10) with terms describing diffusion:

$$\frac{\partial x}{\partial \tau} = a + x^2 y - bx - x + D_x \frac{\partial^2 x}{\partial r^2},$$
$$\frac{\partial y}{\partial \tau} = -x^2 y + bx + D_y \frac{\partial^2 y}{\partial r^2}, \tag{11}$$

Then we obtain a system in which concentration waves arise for certain relationships between the parameters a, b, D_x and D_y. The system proves capable of differentiating.

We assume that morphogens are diffusing—substances released by the cells and acting on the cells. This action reduces to activation or repression of certain genes—above all the regulator genes. It has been shown that this qualitatively explains the events observed in regeneration of hydra. Moreover, the morphogens of hydra have been characterized to a certain extent.[60] The fates of the cells and tissues in a developing embryo are determined specifically by the field of morphogens: the concentrations and diffusion gradients of the functional substances differ in different parts of the embryo. Here not only the position of a cell is essential, but also the time that it exists in some particular zone. Apparently the intercellular signaling in all vertebrates is the same, but the interpretation of these signals varies in the course of evolution.

Thus small changes in the field of morphogens, changes in the site and time of action of the regulator genes, can lead to considerable changes in structure. The cells of humans and chimpanzees are practically identical, but these organisms differ significantly, apparently precisely as a result of differences in the fields of morphogens.

Development passes through a series of stages with transitions resembling phase transitions. The action of a morphogen is a triggering action: a small change in its concentration leads the system from an unstable state to one of the possible stable states. Chemistry is followed by mechanics: the cells move in a directed fashion.

Of course, we cannot consider the presented material to be a finished theory. These are hypotheses that require experimental and modeling, theoretical confirmation. Further development of the theory of evolution involves advances in studying ontogenesis—individual development. These questions require special study (see, in particular, Ref. 61).

A clear example of the action of morphogenetic fields and reading of the PI is the process of segmentation in invertebrates, in particular in flies.[62] This process is being studied intensively, since to a considerable extent it determines the structure of the arthropods and other phyla. The special importance is revealed of the time of turning on and off of chemical factors responsible for the fate of a segment.

As we see, the ontogenesis of the preexisting organisms fixes the direction of evolution, and channelizes it. The genome and the mechanisms that conserve it and alter its structure directly control evolution. The mechanisms of alteration of genomes are independent of any stress by the environment, and thus evolution is channeled inside the organism.[63] The evolution of the nervous system has been studied[64] from this standpoint (see also Ref. 65).

The directionality of evolution is associated with the problem of adaptation—with the answer to the questions "for what purpose?"

Undoubtedly many changes in the course of individual development are adaptive. But others may not be so—they arise as consequences of physical limitations, the architecture of development and the organization of the ancestors.

It is now clear that the question of the number of legs of a terrestrial vertebrate is the question "from what cause?" rather than "for what purpose?" Its answer is now known: because terrestrial vertebrates came from the crossopterygii, which had four corresponding members.

Let us take up an amazing example to which much attention has been paid recently. By examination one cannot distinguish the external sexual organs of the female of the spotted hyena from those of the male. One asks, for what purpose?

One should ask, from what cause? Because in this species the female is appreciably larger than the male (which possibly has an adaptive value), while the growth of an animal is determined by the concentration and activity of hormones. The stated features are determined by an elevated concentration of androgenic hormones in the blood of the female. This is an incidental trait (see the important studies of Gould[66–71]).

For what purpose did Cro-Magnon man need a brain capable of abstract thinking? Perhaps the human brain arose as an incidental trait. This question is still open (see Refs. 72–74). We should emphasize that it is precisely the brain that has allowed humans to overcome the law of noninheritance of acquired traits in social development. Humans inherit the experience of the previous generations—they have books.

A striking example of a nonadaptive trait is the red color of blood (i.e., hemoglobin).

Thus by no means all traits are adaptive. Along with the direct creation of a trait as the result of natural selection, there is the utilization of a trait that earlier had no application or was applied otherwise. Traits can also be antiadaptive: perhaps the giant deer died out precisely because of the excessive weight of its horns (see Refs. 75, 76).

The very existence of nonadaptive traits is a striking demonstration of the directive role of the restrictions imposed by belonging to a definite type of development.

We see that new species do not inherit the adult form of their ancestors. They obtain the complex genetic system and a set of paths of development in which genetics is translated into embryology. These paths restrict the expression of genetic variability—they channel evolution. Natural selection cannot turn a species from the path predetermined by its history—selection acts only on the variants available to it. As Gould[71] wrote, "organisms are not pieces of putty that can be infinitely shaped to any degree, in any direction, but rather amount to complex, elastic structures endowed with innumerable restrictions and possibilities based on inheritance and architecture (both molecular and morphological) . . . Natural selection can be the motive force for changes, but the organism substantially participates in this process by restricting the directions of possible changes."

The course of evolution resembles the operation of self-winding watches. Out of the innumerable multitude of random, disordered movements, the mechanism selects only those that wind the spring.

Just as the watch does not run backwards, evolution is irreversible precisely because it is directional.

5. HISTORY OF THE EYE

As an example of the appearance in evolution of a complex system, let us examine the history of the organ of vision.[77] This example is not random—always, in discussing evolution, nonspecialists are struck by the complexity and perfection of the eye and ask how it could arise.

The biosphere and life owe their existence to sunlight. The radiation in the visible region of the spectrum governs very important biological phenomena—first of all, photosynthesis, which is responsible for the existence of the world of green plants and the atmosphere that they have created, containing oxygen. As a result of this, the kingdom of animals arose and exists.

Light exerts some particular action on a system that absorbs it. As we know, the chlorophylls are substances that absorb light in green plants, in a number of bacteria and algae. Of substantial importance also are the carotenoids and the phycobilins. Figure 7 shows the structure of β-caro-
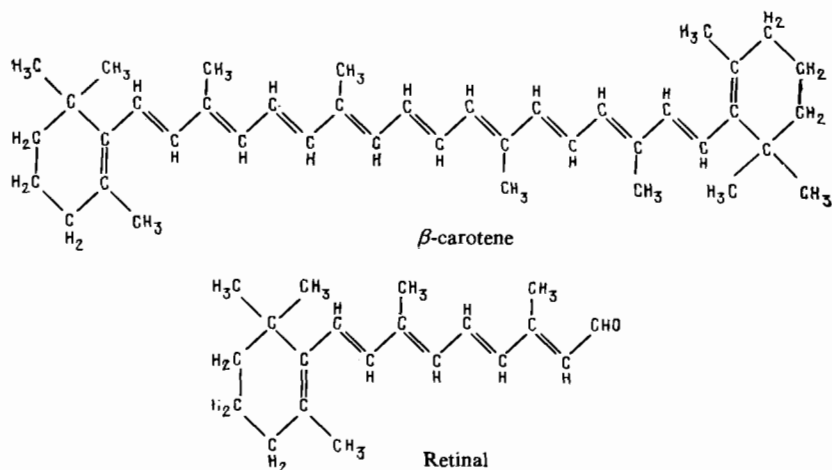
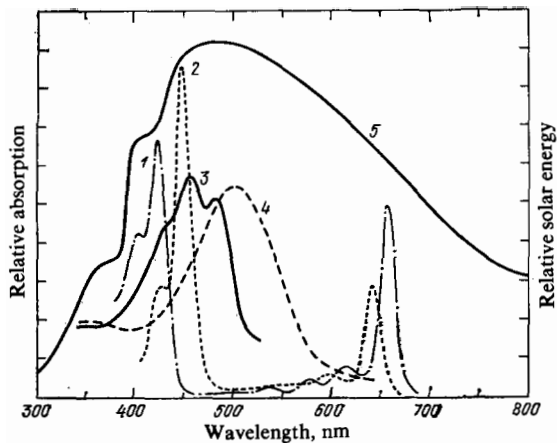β-carotene

Retinal

FIG. 7. Structures of β-carotene and retinal.

FIG. 8. Absorption spectra of chlorophyll a (1), chlorophyll b (2), β-carotene (3), rhodopsin (4), and the spectrum of sunlight (5).[77]

FIG. 9. Photosensitive cell of euglena containing the eyespot-flagellum system.[77]

tene and retinal. The latter substance gives rise to vision; it enters into rhodopsin (see below). Figure 8 shows the absorption spectra of the two chlorophylls, β-carotene, and rhodopsin against the background of the spectrum of sunlight.[77]

We note that also with respect to pigments living nature operates with a limited number of "building blocks." The fundamental structure of chlorophyll is the porphyrin ring, the center of which contains a magnesium atom. The same ring, but with an atom of iron—the heme group—is present in myoglobin, hemoglobin, in the cytochromes, etc. The blood of arthropods contains proteins with atoms of copper, etc. The carotenoids are also universal—they function in the organisms of both plants and animals.

We should start the history of the eye with the phenomena of phototaxis—orientation of the organism or parts of it toward the light. Such is phototropism, say, rotations toward the light of leaves and flowers of plants. As applied to freely moving organisms—to animals, to certain bacteria—one can speak of photomovement. Phototaxis is based on the phenomenon of photoreception—absorption of light by molecules of a pigment organized in some way. The phototropism of the fungus *Phycomyces* has been studied in detail. The photosensitivity is shown by the sporangiophore of this organism, which contains a number of carotenoids. The rotation and bending of the sporangiophore upon illumination involve the response of contractile proteins resembling muscle proteins to photostimulation, which causes a change in the electrochemical potential of specialized cells (see Ref. 77, Chap. VI).

The red halobacteria contain the red protein bacteriorhodopsin—a complex of the protein opsin with retinal (see Figs. 7 and 8). These bacteria live in very salty lakes. They possess a positive phototaxis to visible light and negative to the ultraviolet. Absorption of light by bacteriorhodopsin leads to a chain of events, in particular the desalting of the inner medium of the bacterial cell (see Ref. 7, Sec. 14.7). Bacteriorhodopsin is not only a photosensor, but also a photogenerator, which gives rise to a kind of photocurrent.

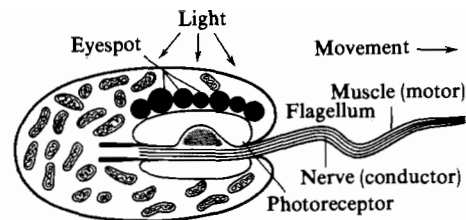The infusoria euglena shows positive phototaxis—it swims toward the light. In this case, in contrast to the halo-

bacteria, the photosensitive substance is concentrated in the form of a photoreceptor organ—the eyespot. The spot in euglena is orange-red, and consists of several granules of dimension from 0.1 to 0.3μm. It is associated with the flagellum by which the euglena moves. Here, as in the case of *Phycomyces*, an interaction is realized similar to the neuromuscular interaction in multicellular animals. The corresponding diagram is shown in Fig. 9.[77] Two pigments participate in light absorption, one of which again is a carotenoid.

The development of the eye in multicellular animals has taken different paths. One can cite four stages—the primitive photoreceptor system (eyespot), the simple image-forming eye (pinhole aperture), the compound eye, and the refractive eye. As had been noted long ago, there are only several possibilities for constructing an organ of vision. Haldane wrote[78]: "There are only four types of eyes if we define the eye as an organ in which light incident in one direction stimulates one nerve fiber. There is the bundle of tubes looking in different directions, and three types analogous to the three well known instruments: the pinhole camera, the ordinary camera with a lens, and the reflecting telescope. A directed series of small steps leads through the type with the pinhole aperture to the type with a lens, and we can very easily understand how this could happen repeatedly." Vision confers great advantages; the eye is an adaptive trait.

Flatworms, in particular planaria, have eyes with pinhole apertures. In the earthworm the light-sensitive cells lie on the surface of the body; each of them has a lens and is surrounded by a neurofibrillar network. The lens is a specialized region of the cuticle, or thickened skin. A structure consisting of a lens and a cluster of photosensitive cells is called a simple eye (ocellus). It is shown in Fig. 10. Many insects have this type of simple eyes.

Thus photosensitive regions arise even in the unicellular animals, and combinations of the neuromuscular type exist in the infusoria. The appearance of a lens initially involved the fortuitous thickening of the superficial tissues—the corresponding mutants acquired advantages.

The second type of optical system is a bundle of tubes. The dimension of the image coincides with the object regardless of the distance. One can examine well only objects equal or smaller in dimensions than this instrument. Distance estimation is impossible. However, if the apertures of the tubes lie on the surface of a sphere or of a segment of it, with the tubes directed toward the center, then the system works much better. The structure of the faceted eye of a number of
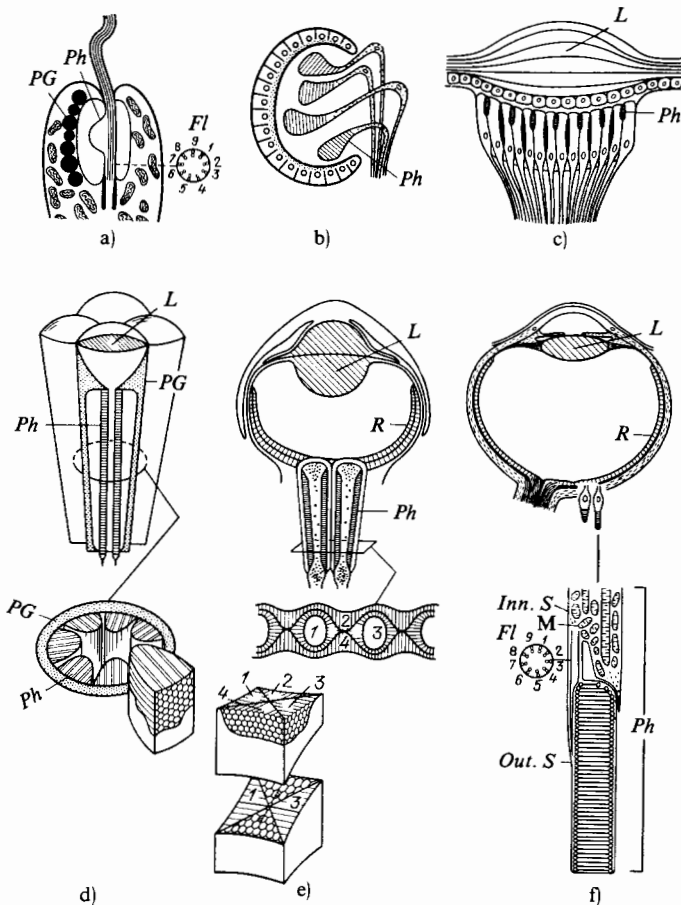
FIG. 10. Phylogenetic development of different types of eyes and the structure of their photoreceptors.[80] a) Eyespot-flagellum in the infusoria; b) simple eye (ocellus) of the flatworm; c) simple eye of an insect; d) compound eye of an arthropod; e) eye of a cephalopod mollusk (1–4—rhabdomeres); f) eye of a vertebrate. L—lens, FL—flagellum, PG—pigment granules, R—retina, Ph—photoreceptor, M—mitochondria, Out. S—outer segment, Inn. S—inner segment.

(see Ref. 6, Chap. 7; Ref. 7, Chap. 14). Skulachev, Ostrovskiĭ, and their associates have shown that the rhodopsin of vertebrates, like bacteriorhodopsin, is a photogenerator.[80] Under the action of light, rhodopsin creates a concentration difference of protons inside and outside the cell. Potential differences arise that are responsible for the appearance of a nerve pulse.

In all living nature the light-sensitive substances are of single type. The evolution of the organ of vision has proceeded by a few different paths fixed by the structure of the starting type of development and natural selection.

Let us present Darwin's words: "When we reflect on these facts, stated here too briefly, on the broad, varied, and graduated set of structures in the eyes of the lower animals, and when we bear in mind how small the number of living forms must be in comparison with those that have become extinct, it ceases to be too great an effort to believe that natural selection could convert the apparatus of an optic nerve covered with pigment and supplied with a transparent membrane into an optical instrument . . . "

6. MOLECULAR EVOLUTION AND THE NEUTRALIST THEORY

Now let us examine the more general questions involved in molecular evolution. We recall the fundamental tenets of molecular biology[81] and molecular biophysics.[7,82]

All the functions of the living cell are governed by proteins. The proteins amount to polypeptide chains built of 20 types of amino-acid residues. The sequence of these residues in a protein is called its primary structure. In most proteins the chains are wrapped into globules—dense structures that are a sort of aperiodic crystal. It is precisely the globule that performs the biological functions of the protein, of which we should deem the most important to be the catalytic one. The protein enzymes serve as catalysts of all biochemical reactions.

The proteins know how to do everything, but they cannot synthesize themselves. The biosynthesis of proteins is performed by the nucleic acids. Deoxyribonucleic acid (DNA) serves as the initial template for assembly of the protein chain from amino acids. DNA (and also ribonucleic acids (RNA)) amount to polymer chains made of four types of links—nucleotides. Thus the nucleic acid is a text written in a four-letter alphabet, while a protein is a text written in a twenty-letter alphabet. The nucleic acid text fixes the protein text. This constitutes the principal function of the gene: a structural gene is a region in a DNA chain responsible for the synthesis of one protein chain. The already-solved problem of the genetic code arises—the correspondence between the sequence of nucleotides in DNA (or RNA) and the sequence of amino-acid residues in the protein chain. The gen-

arthropods is based on this principle. A compound eye forming an image has been established even for the trilobites, which lived in the Cambrian period. The elements of this eye are called ommatidia. They can exceed 2000 in number (in the dragonfly). Each ommatidium in the compound eye contains a corneal lens—a thickening of the cornea, a crystalline cone, and the cells of the retinula with a differentiated light-sensitive structure called the rhabdomere (see Fig. 10). In the fly *Drosophila* the compound eye contains more than 700 ommatidia.

In other branches of the evolutionary tree an eye has arisen similar to that of humans. In the octopus the eye is constructed in the same way as in vertebrate animals, with the difference that the image is focused in the octopus as in a camera by shifting the lens, but in the vertebrates by changing its curvature. Figure 10[77] shows all the cited cases.

The similarity of the eyes of mollusks and vertebrates does not imply that they came from a common ancestor. The overall diagram of biological evolution is shown in Fig. 11.[79] We see how remote the branches are that lead to the vertebrates and the mollusks. The cited resemblance is a striking example of convergence, independent similar development of organisms under similar conditions (in the sea) and the employment of one of several possible pathways of creating an organ of vision.

Different rhodopsins are used in all cases as the photosensitive substances—these are protein complexes of retinal very similar to the bacteriorhodopsin of halophilic bacteria
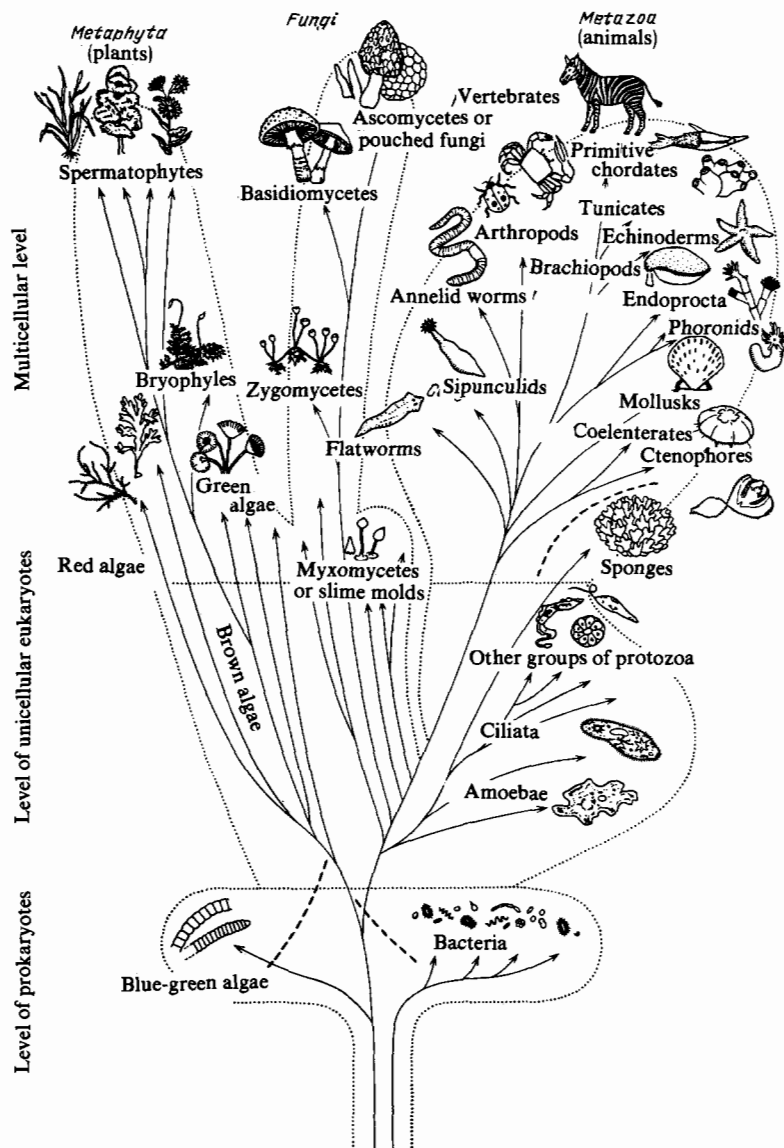
FIG. 11. Diagram of the development of the living world.[79]

etic code is given in Table II. Each amino acid is coded by three nucleotides—a codon. There are 20 amino acids, and

TABLE II. Genetic code. *xyz*—codon; A, C, G, U—nucleotides of RNA; Ala, Arg, etc.—symbols of the amino-acid residues; Term—terminating codons.

x \ y	A	C	G	U	z
A	Lys Asn Lys Asn	Thr	Arg Ser Arg Ser	Ile Ile Met Ile	A C G U
C	Gln His Gln His	Pro	Arg	Leu	A C G U
G	Glu Asp Glu Asp	Ala	Gly	Val	A C G U
U	Term Tyr Term Tyr	Ser	Term Cys Trp Cys	Leu Phe Leu Phe	A C G U

$4^3 = 64$ codons, but three of them are terminal—coding the termination of the protein chain. Thus the code is highly degenerate.

The nucleic acids possess "legislative power," and the proteins "executive power." Genes—programs for protein synthesis—are inherited and evolve. However, natural selection does not act directly on the genes, but on the phenotypic traits of the organism that are determined by the functioning of the proteins.

At present the primary structures (sequences of "letters") are known for several thousand proteins and a multitude of genes. The spatial structure of the globules has been established by x-ray structural analysis for about 200 proteins.

Thus rich potentialities exist for correlating the structure of proteins of a given type and the nucleic acids for many species. One can trace evolution on the molecular level. Such a study has been performed, e.g., by comparing the hemoglobins of different species of vertebrates. Even more valuable data have been obtained by comparing the cytochromes *c* of a number of organisms, beginning with bacteria and ending
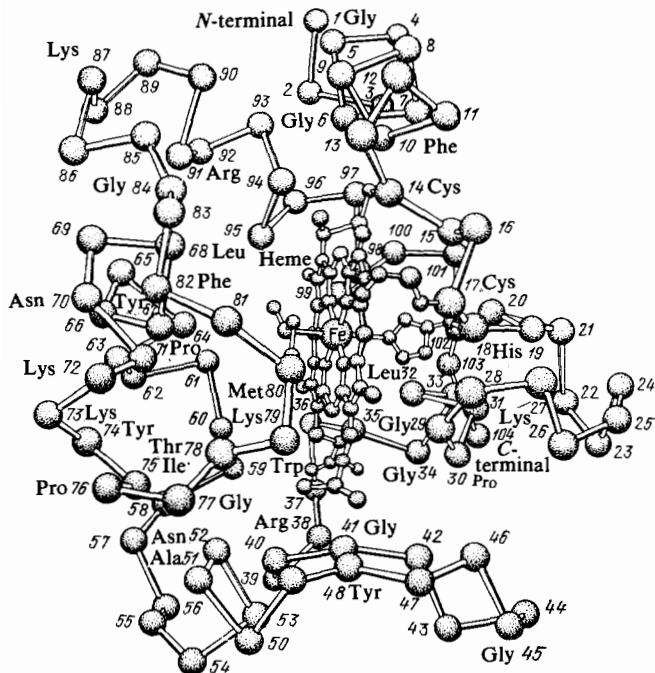
FIG. 12. Spatial structure of horse cytochrome c.

with man. Cytochrome c is the universal protein serving for electron transport in the so-called respiratory chain; its functioning is necessary for the vital activity of aerobic organisms.

Figure 12 shows the spatial structure of horse cytochrome c as established by x-ray structural analysis. The heme group mentioned above lies in the center of the molecule.

Comparison of the amino-acid compositions and primary structures of the cytochromes c enables one to construct the genealogical tree of these proteins, similar to the evolutionary tree of the corresponding organisms. This tree is shown in Fig. 13, which shows also the matrix of numbers of amino-acid residues by which different species differ from one another (Ref. 83; see also Ref. 84). Thus, the cytochrome c of humans differs from that of the dog in 11 residues, and from the cytochrome c of baker's yeast in 45 residues.

Thus one can find molecular measures of the closeness of species to one another. These measures are relative; when found for different proteins they do not fully coincide with one another. Nevertheless the proteins of remote species always differ more from one another than those of similar species.

One can naturally think that these differences are determined by natural selection acting also on the molecular level. In other words, each substitution of an amino-acid residue in a protein chain (in turn determined by the substitution of one or more nucleotides in a gene—in DNA) has an adaptive value. However, we have already seen that not all in biology is adaptive.

In 1968 Kimura showed for the first time that at least an appreciable fraction of such substitutions—point mutations—is selectively neutral.[85] King and Jukes[86] indepen-
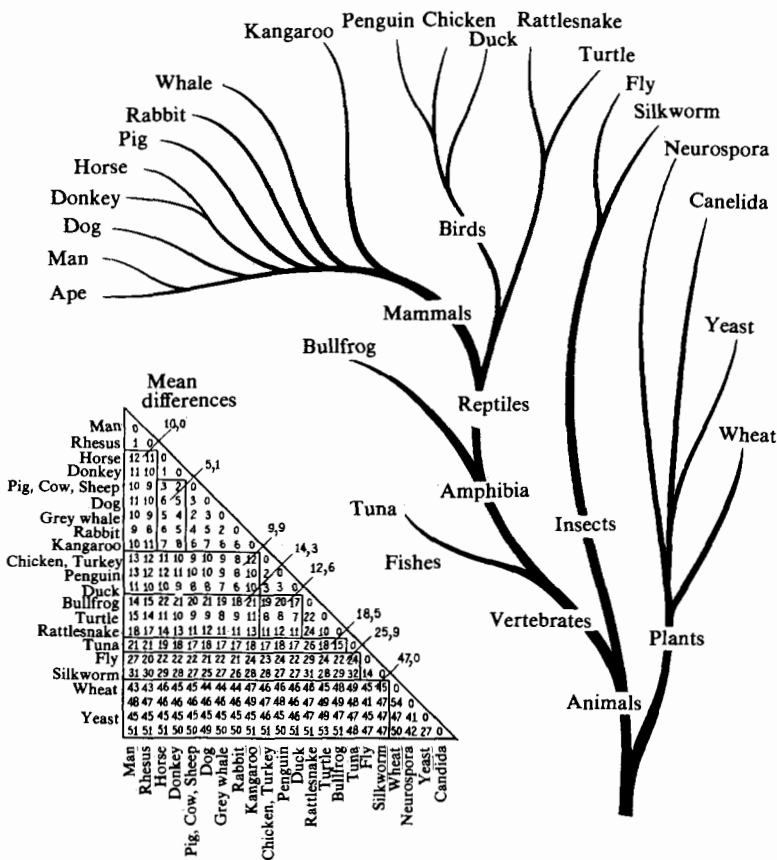

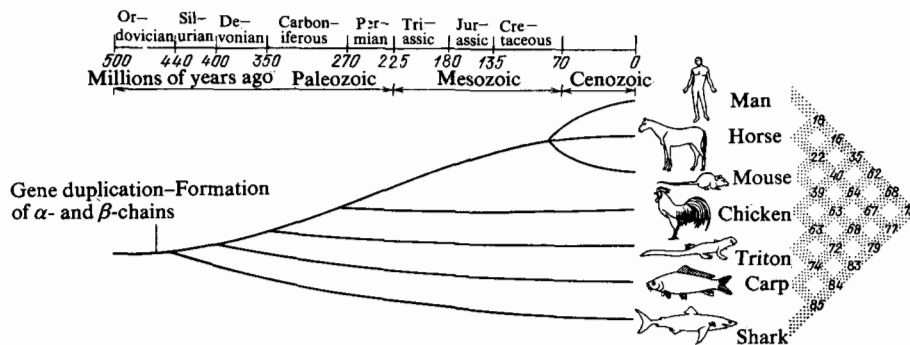FIG. 13. Phylogenetic tree of the cytochromes c (Dickerson).

FIG. 14. Phylogenetic tree of the hemoglobins α for seven vertebrates.[87]

dently arrived at the same conclusion; reviews are given in Refs. 87 and 88.

According to Kimura, a comparative analysis of mutational substitutions in proteins and nucleic acids shows that: 1) for a given protein the rate of substitutions of amino-acid residues is approximately the same for different evolutionary lines; 2) these substitutions are random in character; 3) the rate of substitutions on the DNA level is very high, reaching one substitution of a nucleotide per genome every two years (in the mammalian line).

This implies that most of the nucleotide substitutions in the course of evolution must result from random fixation of neutral or almost neutral mutants. The method of gel electrophoresis has established the polymorphism of many proteins: in a particular organism a given protein can appear in a number of forms differing in primary structure, but not differing too much from one another functionally. The polymorphism of proteins also serves as an expression of the neutrality of mutations.

Thus natural selection, which undoubtedly acts at the level of phenotypes, does not directly affect the primary structure of DNA and proteins. The constancy of the rate of evolution is demonstrated, e.g., by the structure of the hemoglobins (Hb). The Hb molecule of the bony fishes and the higher vertebrates is built in the form of a tetramer consisting of two α globules and two β globules. In mammals replacements of amino acids in the α chain, which contains 141 amino acids, occur at the rate of about one substitution per 7×10^6 years (or one substitution per amino acid per 10^9 years). Figure 14 shows the phylogenetic tree of Hb α for seven vertebrates. The numbers in the matrix on the right are the differences in the primary structure in numbers of substitutions. The approximate constancy of the numbers on the diagonals running upward to the right, show this constancy.

These ideas have aroused sharp objections (and sometimes arouse them even now). The "selectionists," in criticizing the "neutralists," have stated that a mutant allele can propagate in a population only if it has a selective advantage. However, if the mutant is selectively equivalent to those previously existing, then its fate depends on chance, its frequency fluctuates, and it can be fully represented in the following generations.

Let us study the genome of an organism. The single (haploid) set of human chromosomes contains about

3.5×10^9 nucleotides. Their rate of mutational substitutions is of the order of 10^{-8} per generation. Hence we can assume that each new mutation arises at a different point.

Let v be the rate of mutations per gamete per generation. In a population of N individuals, $2Nv$ mutants arise in each generation (the factor 2 arises because each individual possesses a double set of genes). If u is the probability that an individual mutation will be fixed, then in a prolonged process the rate of mutational substitutions is

$$k = 2Nvu. \tag{12}$$

If the mutant is selectively neutral, then $u = 1/2N$, since any one of the $2N$ genes is fixed with equal probability. In this case we obtain

$$k = v. \tag{13}$$

If the mutant has a small selective advantage (coefficient of selection) s, then $u \approx s$, and we obtain

$$k = 4Nsv. \tag{14}$$

The coefficient of selection s is calculated as follows. The survival rate of the genotype is the ratio of its abundance in the population after selection to that before selection. The relative fitness w of the genotype is the ratio of the survival rate of the given genotype to that of the genotype for which this quantity is maximal. Evidently we have $0 \leqslant w \leqslant 1$. The coefficient s equals $1 - w$, with $0 \leqslant s \leqslant 1$.

The observed constancy of s agrees with the relationship (13). It is hard to imagine that the product Nsv would prove to be the same for different evolutionary branches.

Further, it has been established that mutations bearing insignificant harm, i.e., characterized by a small negative coefficient of selection s, must behave like neutral mutations if $|s| \leqslant 1/2N_e$.[89-91] Here N_e is the effective numerical size of the population.

Different proteins evolve at different rates—the more ancient and universal proteins evolve more slowly than the proteins that have arisen later. We present the pertinent Table III.[87]

We must stress that, owing to the degeneracy of the code, many of the substitutions of the third nucleotide z in the codon xyz are "silent mutations" that do not lead to an amino-acid substitution (see Table II). However, such mutations are of evolutionary importance, since subsequent mutation of paired degenerate codons leads to different results.

TABLE III. Rate of evolution in terms of the number of amino-acid substitutions per amino acid per 10^9 years.

Protein	Rate	Protein	Rate
Fibrinopeptides	9.0	Animal lysozyme	1.0
Pancreatic ribonuclease	3.3	Insulin	0.4
Hemoglobin	1.4	Cytochrome c	0.3
Myoglobin	1.3	Histone IV	0.006

What does the physical meaning of the neutralist theory consist in? (See Ref. 92.)

As we have already stated, only the primary structure of a protein is coded genetically, while natural selection acts on phenotypes, i.e., on the biological functions of organisms at all levels of their structure down to the molecular level. If there were no connection between the primary structure of a protein and its biological function, molecular biology and molecular genetics would lose meaning. Undoubtedly there is a connection. However, is it unambiguous?

Essentially we are dealing with two correlations—the correlation of the primary structure of a protein and its spatial structure and the correlation of the spatial structure and the biological function of the protein.

We can consider it established that these correlations are not unambiguous, but degenerate. The information on the spatial structure of proteins indicates that different primary structures can yield the same spatial structure. For example, this has been shown for a large number of globins.[93] All these proteins contain the functional heme group immersed in a cavity of the molecule. Their primary structures strongly differ, but their spatial structure are very similar.

Similarity of spatial structures has also been established for the cytochromes c. The chains of this protein have different lengths in different species of bacteria, differing from the chain length in the vertebrates. The primary structures also strongly differ, but the spatial structures are similar to one another.[94]

The physical meaning of the neutralist theory reduces to this ambiguity.

An essential and independent argument favoring the neutralist theory is the "stability to interference" of the genetic code, which was first established in Ref. 95 (see also Refs. 7 and 82). The code is constructed by nature in such a way that, in single substitutions of nucleotides in codons, amino-acid residues are replaced much more often by residues of similar properties than by residues with sharp differences. Replacements of the first type can be quite neutral. The replacement of one residue—the anionic amino acid Glu by the neutral amino acid Val in the β-chain of human hemoglobin, which contains 146 residues, leads to a severe blood disease—sickle-cell anemia.

Why do some proteins evolve by undergoing neutral substitutions more rapidly and others more slowly (see Table III)?

A protein is not a homogeneous globule, but a complex molecule, a kind of machine. A protein—enzyme—contains an active center, a grouping of amino acids that bind the molecules whose transformation is being catalyzed. The function of a protein is localized in its active center. In the case of an enzyme, this is where the chemical rearrangement of the substrate occurs, and its electron shell is rearranged. The remaining "passive" part of the protein molecule plays the role of a reaction medium, and conformational movements occur in it, i.e., rotations of atomic groups about the single C–C, C–N, and C–O bonds. The biological, i.e., enzymatic, function of a protein results from interaction of the electronic and conformational degrees of freedom of the system—electronic-conformational interaction (ECI).[7,82,96] Evidently the "active" part of the protein must have a more fixed structure than the "passive" part. This is so. The relative evolutionary constancy of the active center and its immediate environment has been established for a number of proteins.[82,84,94] It has been shown that in Hb the "passive" part evolves about 10 times faster than the "active" part.

The rate of evolution of a protein is determined by the restrictions imposed on its structure—by the fraction of the "active" subsystem. Thus, in the case of the practically invariant histone IV (see Table III), its whole molecule is functional, or "active." Crudely speaking, the restrictions of the rate of neutral evolution are greater as the ratio of the numbers of amino-acid residues in the "active" to the "passive" subsystems of the protein increases.

An important substantiation of the neutralist theory has been obtained in a recent study by O. B. Ptitsyn.[97] As is well known, averaging over the primary structures of globular proteins yields practically no statistically reliable differences from a random distribution for the amino-acid residues and groups of them along the chain. Ptitsyn showed that this conclusion holds true also in studying the higher levels of structural organization of proteins.

In a protein globule the chain forms the elements of the secondary structure of the protein, α-helices, β-"ribbons," and disordered regions. Ptitsyn showed that the distribution of lengths of the α-helices, β-ribbons, and disordered loops in proteins practically coincides with that for a statistical copolymer with a random distribution of links. This also holds for clusters formed by α- and β-regions. Thus a protein amounts to an "edited statistical copolymer." In the "active" part of the protein there is no longer randomness—it is "edited" by natural selection. The randomness of the "passive" part implies that the substitutions in it are neutral in type.

Evidently it is precisely owing to the relative constancy of the "active" subsystem that the substitutions observed in the evolutionary trees pertain preferentially to the "passive" part. Kimura's conclusions are fully justified.

We can assume that the initial appearance of a gene—a region of DNA coding some protein—was to a considerable degree a matter of chance. Correspondingly the primary structure of the protein was fixed randomly, and was then subject to "editing." The "edited" part of the protein is fixed, and neutral random substitutions can occur in the rest. The evolutionary reasons for the polymorphism of proteins—the existence of isoenzymes—are understandable.

Neutralism follows directly from the defining, controlling role of the already developed type of structure and the means of changing it. These factors act at all levels down to

the molecular level. If a definite type of protein has taken shape that performs a function important to the organism, say, hemoglobin in all the vertebrates, then for the given type of organisms such a protein either must remain invariant or its changes must be neutral.

The neutralist theory does not contradict Darwin's theory. On the contrary, it explains the considerable rate of evolution. If a rigid primary structure with fixation of each of its residues were needed for successful functioning of a protein, then this would require far more time than the evolutionary fixation of only those residues that enter into the active center. Besides, the fixation of the active part is not absolutely rigid—replacements of amino-acid residues by ones related to them can and actually do occur.

To speak figuratively, the editing of a text takes less time and effort than writing it.

7. DYNAMICS OF GENES

It is usually assumed that the genes are immobile, and that they can change only as the result of point mutations. Actually the situation differs.

We have already seen that the structure of the organism depends not only on the very existence of definite genes, and thus on definite proteins, but also on the site and time of action of the genes. The amount of a given protein, if its synthesis is not blocked by the regulatory system, is essential for the organism. Naturally it depends on the number of identical genes programming this protein. The number of repetitions in the genomes of eukaryotes can be quite considerable—it can reach tens of thousands of copies of the nucleotide sequence. This holds both for structural and nonstructural genes.

DNA molecules have a highly complex and specific structure. Segments of DNA exist that can change their position in the genome.[98] A widespread distribution has been found in bacteria of different factors that shift around in the genome. Such are the plasmids, the transposons, and certain bacterial viruses—the phages. Similar phenomena are also observed among the eukaryotes. The transposons are regions of DNA capable of shifting around in the genome and "jumping over" to a new site.

The plasmids are small supplementary chromosomes capable of transferring from cell to cell and being incorporated into the genome. Among the bacteriophages are known the so-called lysogenic or temperate phages, whose DNA is incorporated into the genome of cells infected with the phage.

It has been established that the factors that determine the resistance of bacteria to antibiotics (see above, Sec. 4) and to other pharmaceutical substances are associated in a number of cases with plasmids and transposons. The enzymes coded by these regions of DNA determine the resistance. The resistance of higher organisms—of insects to DDT and to organophosphorus compounds—that has spread throughout the world in a short time apparently has an analogous origin.

The translocation of mobile elements causes mutations of all known phyla. It can be a factor of parallel, or conver-

gent variability. It can play an important role in regulating the activity of genes by leading to enhanced synthesis of the corresponding enzymes.

The dynamic properties of genes govern important phenomena of biological development different from phylogenesis and ontogenesis. These phenomena are the appearance of malignant neoplasms (cancerogenesis) and the appearance of immunity. Oncogenic viruses have the capability of incorporating their DNA into the genome of the host cell. Integration of the provirus is realized, with subsequent multiplication, and can be stimulated by various factors.

Viruses can transport genetic material of certain cells into others. This is the phenomenon of transduction, which has long been known in molecular biology (see Ref. 81 and 82).

Also ordinary genes that have entered into a special state can translocate through the genome; these are the so-called unstable or supermutable genes. Thus it has been found that in a certain line of drosophila two neighboring genes responsible for the color and shape of the eyes can translocate to different sites on the chromosomes.

Owing to the possible transport of plasmids and transducing viruses, a flux of genes can occur even between distant organisms. The number of different plasmids is practically unbounded. To exaggerate the situation somewhat, one can speak of a unitary gene fund of all bacteria and even of a single gene fund of all life (Khesin). For example, perhaps the similarity of the globins of animals and the legoglobin protein that participates in fixing atmospheric nitrogen by plants is explained by a gene transport that occurred at some time from animals to plants. Cases are known of transfer of genetic material from prokaryotes to eukaryotes, and also vice versa. It has been established that certain plasmids of bacteria cause tumors in plants. This implies that one might obtain in this way different species of plants. On the possibility of jumping of genes among different eukaryotes, see Refs. 98 and 99.

We can consider it established that the expression of the genes of eukaryotes is determined by a broad variety of mechanisms, including loss, multiplication, and rearrangement of genes. Families of multigenes—repeated genes—regulate the amount of proteins being synthesized, their variety, and their time of synthesis.[100]

Owing to the translocation of genes, situations arise in which a sort of "battery" of genes is created—sets of them jointly controlled by a single factor.

In principle transfer of genetic material is also possible from somatic to sexual cells. The possibility has been discussed of the natural selection of somatic mutations and their transfer to the gametes. Does this imply the inheritance of acquired traits?[101] Evidently not, since the stated transfer is not a transfer of adequate information.

The mobility of genes combined with their multiplicity—with their copies—can play a specific role in speciation. These phenomena are called molecular drift, and in principle they define a mechanism of evolution different from natural selection and drift of genes (cf. Sec. 3).

Eukaryotes have a large excess of DNA over that neces-

sary for protein synthesis. A large part of this excess DNA consists in multiple copies. Remarkably, individual families of copies are more similar within a species than between related species. Thus a sort of homogenization of the chromosomes with respect to copies is realized within a species. It is determined by the constant rearrangements of the repeated sequences caused by non-identical interchromosomal exchange (crossing-over), by transfer of transposons and gene conversion—directed or random nonequivalence of corresponding alleles. Possibilities arise of deviation from Mendel's laws. Consequently "concerted" development of a population in a genetic direction can occur that differs from that in a closely related species. Figure 15 shows a diagram of possible ways of homogenization of chromosomes by molecular drift. One can show that molecular drift can play a role in evolution, with an insignificant directionality in gene transfer decisively accelerating evolution. The evolutionary relationships of a number of related species of the fly *Drosophila* have been interpreted with the aid of the theory of molecular drift. These problems require further experimental and theoretical studies (see Refs. 102 and 103).

Gene transfer yields important information on cancerogenesis. The appropriate experiments have been set up in tissue cultures, and it was possible to identify the oncogenic transforming genes.[104,105]

Naturally, the corresponding phenomena in prokaryotes and viruses have been studied thus far much better than in eukaryotes. In closing this section, let us take up the well studied case of gene switching in a bacteriophage.[106]

Some strains of the bacterium *Escherichia coli* (intestinal bacterium) contain a "dormant" temperate virus, the so-called λ-phage. The genome of the phage is incorporated into the genome of the bacterium and does not reveal itself. However, upon induction—with ultraviolet irradiation and certain chemical agents—the virus begins to multiply and destroy the cells. The DNA of λ-phage contains 35–40 genes that code its proteins.

In the "dormant" state in the prophage only one protein is synthesized, the so-called λ-repressor. It turns off the action of all the rest of the genes that code other proteins of the phage. However, the λ-repressor stimulates the operation of the gene responsible for its own synthesis.

If the phage is induced and multiplies, another protein regulator arises, called *cro*, that turns off the gene responsible for the λ-repressor. It has been established that both the λ-repressor and *cro* are bound in their action to the very same region of λ-DNA, called the rightward operator (o_R). Switching of o_R activates the former or latter gene. This is
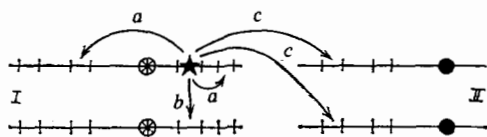

FIG. 15. Diagram of molecular drift.[102] *a*—intrachromosomal drift; *b*—drift between homologous chromosomes; *c*—drift between nonhomologous chromosomes.
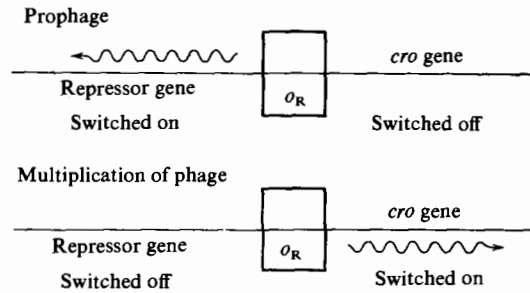

FIG. 16. Diagram of the switching of the genes of λ-phage.[106]

shown schematically in Fig. 16. The molecular mechanism of this switching reduces to the fact that the molecule of the enzyme RNA polymerase ultimately responsible for protein synthesis moves to the right or left along the DNA of the phage.

This example strikingly shows the role of the processes of regulation in the development of living systems. The changes in regulation caused by translocation of genetic material can be decisive. It is also evident on the molecular level that evolution is far from being reduced to the natural selection of point mutations in genomes. Of course, the phenomena described here require a special treatment not appropriate for the pages of Uspekhi Fizicheskikh Nauk. Yet it is clear from what we have presented that the tempo of directed evolution is fixed by the molecular basis of development. Changes in the genome are one of the factors of ontogenesis, in which the most important role is played by the regulation of the activity of the genes realized by the interaction with DNA of proteins—repressors, activators, etc.

A considerable part of the knowledge in this field has been gained by R. B. Khesin and G. P. Georgiev (see Ref. 98).

As Khesin writes,[98] "the basis of life is heredity—the exact reproduction of the genome, its stability. But development, whether evolutionary or ontogenetic, is impossible without changes in the genome . . . the problem of the inconstancy of the genome is now one of the important problems of molecular genetics, especially of the higher organisms. Its development must reveal the molecular bases of many biological phenomena that we observe in individual development and in evolution."

8. INFORMATIONAL ASPECTS OF EVOLUTION

In biological phenomena we encounter the creation, coding, transfer, decoding, reception, and storing of information. The study of the informational aspects of biological evolution is instructive.

In Shmal'gauzen's work,[107] the theory of evolution was translated for the first time into the language of ordinary information theory. Natural selection was presented as a transformation of inverse information. This is transformed on the level of organization of individuals with the aid of phenotypes into genetic information transmitted by the chromosomes. This language of the theory of evolution proves useful; by using it one can explain and deepen its concepts. Later Gatlin undertook an attempt at informational interpretation of evolution in mathematical form.[108]

But Shmal'gauzen noted that "contemporary information theory does not possess methods for evaluating the quality of information, while in biology this frequently has decisive significance. In obtaining information from the external environment, the organism primarily assesses it for quality" (Ref. 107, p. 203).

The problem of the quality, meaning, content, or value of information has naturally become an object of study in biophysics.[6,7,109] The essential ideas on the value of information had been previously formulated in the studies of Bongar,[110] Stratanovich,[111] and others.

Evidently the concept of the "value of information" can be defined only in connection with the reception of information: the measure of the value of information is the consequences of its reception by the receiving system. The reception, and hence the memorization of information, is an irreversible process realizable when the initial state of the receptor is unstable. When the latter receives the information, it transforms to a new, relatively stable state. Thus it is impossible to give a universal definition for the value of information. On the contrary, the amount of information, as treated independently of reception, is universal (see, e.g., Ref. 112). Consequently the concept of the level of reception enters into the definition of the value of information, and involves, in particular, the store of previously fixed information—the thesaurus of the receptor.

No thermodynamic analysis of reception and the value of information has been performed. Here we encounter irreversible processes characterized by long-term memory, i.e., practically infinite relaxation times.

What we have said pertains also to the creation of new information. As we have already said (see Sec. 2), the problem is that of memorization of a random selection.[15]

Independently of the problems of the not yet constructed theory, one can give a provisional definition of the value of information as the degree of its nonredundancy and irreplaceability.[7,109] Redundant, repeated information is of no value for the receptor.

Upon introducing this concept of value, we arrive at the conclusion that it increases in the course of ontogenesis and phylogenesis. Let us consider ontogenesis. In the early stages of development of a triton, a certain region of the embryo is responsible for forming an eye. This region is the presumptive eye. If one transplants it into an embryo existing in a later stage of development, the fate of the presumptive eye will depend on the site of transplantation—in the head of the host it forms a brain or eye, while in other regions it forms the organs and tissues characteristic of these regions in normal development. Yet at a later stage the presumptive eye becomes a determined eye—the corresponding region forms an eye when transplanted to any site in the embryo. Totipotency of the region is replaced by unipotency. That is, noninterchangeability arises.

In phylogenesis the divergence of species coming from a common ancestor implies an increase of noninterchangeability, and an increased value of the genetic information.

If the value increases in evolution, then we can suppose that this occurs also on the molecular level. One can compose a scale of values of amino-acid residues in proteins, starting from their mutual replaceability in mutations. The value increases as an amino acid becomes more irreplaceable. By using this scale, it has been possible to show that the total value of the amino-acid residues in the cytochromes c actually increases approximately in accordance with the evolutionary tree in the mammalian and avian series.[7,113] However, this is not true for hemoglobin—in line with the neutralist theory the evolutionary substitutions are random in character. We have seen that the more ancient and universal protein, cytochrome c, is subject to a lesser degree to neutral mutations than hemoglobin is. Precisely for this reason an increase in irreplaceability of amino acids is observed for cytochrome c and not for hemoglobin. It has been shown that the evolutionary increase in the value of proteins requires the presence of a store of residues possessing low value—high replaceability.[114]

The principle of evolutionary increase in complexity of biological systems has been proposed in the literature (see Ref. 115). Here one must rigorously define the concept of complexity. Such a definition has been given by Kolmogorov[116] (see also Ref. 117). The complexity of an object is the minimal number of binary symbols containing information on the object that suffices for reproducing (decoding) it. In other words, the complexity is the length expressed in bits of the most economical program that generates the message concerning the object.

The most complex systems in nature are individual, living organisms, and among them—man. Each individual is unique and cannot be represented by an abbreviated program. This pertains also to the creative works of man, to the works of literature and art.

However, each organism is not only an individual. It is a representative of a kingdom, a phylum, a class, an order, a family, a genus, and a species (cf. Sec. 3). Evidently the complexity increases from the kingdom to the species. Within the limits of each taxon "there are no irreplaceables," all representatives of the given species are mutually replaceable, and are described by the very same minimal program.

We see that the concept of complexity is relative. For a biologist the brain of a steer is a very complex system whose description requires thousands of bits, but for the butcher the description of the same brain requires no more than five bits, since the brain is only one of about thirty parts of the body of the steer that enter into food. The problem is that of different levels of reception, and of the relative value of information. It turns out that complexity is equivalent to irreplaceability, or nonredundancy at the given level of reception. What is irreplaceable is complex. And the value of information and the complexity increase from the kingdom to the species and reach a maximum in the individual.

At the same time, the concept of value is richer than the concept of complexity. Complexity refers to the object as a whole, value also exists in individual elements of the object. Complexity characterizes the structure. Value also expresses the function.

The complexity indeed usually increases in evolution, but converse situations are also known, e.g., transformation to a parasitic form of life.

The principle of increase in value emphasizes the direc-

tionality and irreversibility of biological evolution.[44,118]

Increase in value also involves the increased power of biological systems to select valuable information. Such a selection does not require additional expenditures of energy—the minimum energy value of one bit of information is $kT \ln 2$, independently of the value of this information (see Refs. 7 and 113).

9. CONCLUSION

Let us draw some conclusions. The origin of life and the subsequent biological evolution are phenomena of growth of order in an open system far from equilibrium, a dissipative system. An increase in fluctuations is realized up to the macroscopic level, owing to the efflux of entropy into the surrounding environment.

The foundations of Darwin's theory remain firm—the mechanism of evolution is reduced to the natural selection of the fittest organisms. The material for selection is random mutations.

We should consider completely erroneous the views that evolution involves a sorting of all the possible point mutations in genes, the probability of such mutations being very small. If this were so, evolution would lack both material and time. The fact that there is enough of both is proved not only by the very existence of the modern biosphere in all its variety, but also by a number of arguments.

Natural selection deals with highly heterogeneous populations in which the degree of heterozygosity is reckoned in percents and tens of percent. This furnishes sufficient material for evolution.

Evolution has a directional, irreversible character. Usually one speaks of the randomness of mutations and the directionality of natural selection. But there is a second, no less powerful factor that channels evolution. This is the type of structure and development of the organism that has already taken shape up to the time of selection.

Besides, the significance of this factor was well understood by Darwin, who wrote:

"We clearly see that the nature of the conditions has a subordinate meaning as compared with the nature of the organism in determining each particular form of change—perhaps no more significance that the nature of the spark that ignites a mass of combustible material has for determining the nature of the flame."

And the stages of ontogenetic development, both speciation and macroevolution, have the character of nonequilibrium phase transitions that occur more or less sharply. Such transitions occur in dissipative systems that possess the properties of cooperativity and autocatalysis. Different species behave in different ways—both gradual changes and punctuated equilibrium are realized.

Owing to the directionality of evolution as fixed by the type of structure and development, far from all of the traits of organisms have adaptive value, and the question "for what purpose?" in biology often has no meaning.

The views formulated here are valid also on the molecular level of structure. Let us assume that a randomly defined primary structure of a gene has taken shape—the DNA and

a definite primary structure of the protein. Thus a certain type of structure has been fixed. A considerable fraction of the mutational substitutions in the DNA and of the corresponding ones in the protein is neutral. This pertains primarily to the "passive" part of the protein. Here the type of structure that has taken shape and has biological significance is conserved. The neutralist theory shows that the rate of real evolutionary changes on the molecular level can be considerable, since it is determined by the point mutations only in the "passive" part of the protein molecule. The physical meaning is obvious of the neutralist theory, which reduces to a degenerate correspondence between the primary structure of the protein and its biological function. Neutral substitutions realize biologically functional structures that match the initially formed type of structure.

A number of phenomena have been found in recent years that indicate the dynamic nature and mobility of genes. These phenomena, as well as the multiple copies of genes, apparently have an important significance and govern the rapid rate of evolution. Here the genes are especially essential that program the synthesis of regulator proteins and peptides. Perhaps the differences between species are determined to a greater extent by the differences in regulation than by the differences in structure of proteins. Not only the structure, but also the time and site of action of the molecules are important.

The study of evolution using the concepts of information theory enables us to formulate with great clarity the directionality and irreversibility of evolution. In biological development the value of information, understood as its irreplaceability, increases.

Thus evolution, which started randomly, later on is controlled and channeled, adapting to the changing ecological conditions, in which the evolving population itself is a part of an ecosystem, part of a biogeocenosis. We can state with assurance that if life were to arise and develop anew, the path of evolution would be completely different. We are dealing with a network formed from complex Markov chains whose stochastic matrices contain many zeros, since mutations incompatible with the type of development that has taken shape drop out.

The presented material implies that a physicomathematical modeling, that is to some degree of evolution complete, is as yet difficult. This does not mean that informative models do not exist that convincingly demonstrate the possibility of evolution and the lack of a need for any new physics for understanding it. But our knowledge does not yet suffice for a sufficiently general model. Indeed, a unified quantitative theory must take into account:

natural selection,

the controlling significance of the type of structure and development,

the role of point mutations,

the significance of the dynamics of genes.

All these branches of biology are far from completion, and are being studied in detail, in particular, with the use of models.

But in one way or another, the current state of the theory of evolutionary biology indicates the correctness of Dar-

win's theory and—qualitatively—that there has been enough material and time for evolution.

SOME BIOLOGICAL TERMS

Adaptation—creation or existence of traits that under the given conditions of the environment prove advantageous for the individual or the population, and owing to which the organism acquires the ability to exist in the given environment.

Aerobic organisms—organisms that require oxygen for respiration.

Alleles, allelic genes—mutant genes giving rise to differences in organisms and localized in homologous (equivalent) regions of the chromosomes. For many genes, two alleles are known, one of which, the "wild-type allele" is often dominant over the other.

Allopatry, allopatric species formation—geographic separation of populations. Populations inhabiting different sites are called allopatric. Such division of populations is one of the causes of speciation.

Androgenic hormones—male sex hormones, which stimulate the development and conservation of male sex traits and participate also in stimulating growth.

Aromorphosis—development of groups (populations) along a pathway into a different adaptive zone, i.e., into a different environment that requires a change in adaptation.

Convergence—independent development of similar structures performing a similar function in different animals not related to one another.

Crossing-over—a mechanism leading to gene exchange between longitudinal parts (chromatids) of homologous chromosomes. Crossing-over arises upon breaking and reunion of the ends of the break in a different order.

Cuticle—the hard outer covering of a number of invertebrates, generated by the epithelial cells lying under it.

Ecological niche—a concept combining physical, chemical, physiological, and biotic factors necessary to an organism for living. The ecological niche characterizes the position of the organism in the community, and is determined by the adaptation of the organism, and its physiological reactions and behavior.

Eukaryotes—organisms whose cells contain nuclei, in contrast to prokaryotes.

Gametes—sexual cells: male (spermatozoa) and female (oocytes).

Gene drift—considerable shifts in the frequency of alleles that occur randomly in small populations.

Genome—the set of genes of an individual.

Genotype—the set of all hereditary factors of an organism that enter into the genome.

Globins—a number of proteins containing the heme group, i.e., a porphyrin ring with side-chains, the center of which contains an iron ion. The globins include myoglobin, hemoglobin, etc.

Heterozygote—an individual developing from two gametes differing in their genes. Usually one has in mind an individual having nonidentical alleles (e.g., Aa) in one or several pairs of alleles.

Homozygote—an individual developing from two gametes with identical genes. Usually one has in mind an individual having identical alleles (e.g., AA, aa).

Idioadaptation—according to Severtsov, "changes of an adaptive character, all adaptations to strictly defined conditions of the environment that do not increase the overall energy of vital activity," in contrast to aromorphoses; improvement of adaptation without radical changes, e.g., protective coloration.

Karyotype—the set of chromosomes of the organism, its diploid set as determined by the size, shape, and number of chromosomes, an important characteristic of a biological species.

Macroevolution—evolution of major groups, leading to the appearance of new genera, families, orders, classes, and phyla.

Meiosis—cell division with a twofold reduction in the number of chromosomes leading to the formation of gametes.

Microevolution—evolutionary changes within the limits of a population. Species formation is usually included in microevolution, but some authors treat this process separately from microevolution (Grant).

Mitosis—cell division with doubling of the chromosomes.

Ontogenesis—development of an individual from the stage of the fertilized egg to the stage of sexual maturity.

Phenotype—the set of structures and functions of an organism determined both by its genotype and by the conditions of life and development.

Phylogenesis—evolution of a species.

Prokaryotes—unicellular nonnucleated organisms—bacteria and cyanobacteria.

Recombinations—formation of new combinations of genes in the course of meiosis and mitosis. Recombination results from the splitting of allelic pairs and crossing-over.

Reproductive isolation—impossibility of crossing arising from the characteristics of the organisms themselves. Owing to r. i., populations can inhabit the same territory without exchanging genes.

Sympatry, sympatric species formation—inhabitation of different populations in the same region. Speciation results from reproductive isolation and from other causes.

Soma, somatic cells—any cells of a multicellular organism except the sexual cells.

Taxons—units of the systematics of living organisms: species, genera, families, etc.

[1]W. Ebeling and R. Feistel, Physik der Selbstorganisation und Evolution (Physics of Self-Organization and Evolution), Akademie-Verlag, Berlin, 1982.

[2]M. Eigen, Samoorganizatsiya materii i évolyutsiya biologicheskikh makromolekul (Self-Organization of Matter and the Evolution of Biological Macromolecules), Mir, M., 1973.

[3]M. Eigen and P. Shuster, Gipertsikl (The Hypercycle), Mir, M., 1982.

[4]M. V. Vol'kenshtein, in: Metodologicheskie i teoreticheskie problemy biofiziki (Methodological and Theoretical Problems of Biophysics), Nauka, M., 1979 (Engl. Transl., Biophysics, Mir, M., 1983).

[5]B. M. Mednikov, Aksiomy biologii (Axioms of Biology), Znanie, M., 1982.

[6]M. V. Vol'kenshtein, Obshchaya biofizika, Nauka, M., 1978 (Engl. Transl., General Biophysics, Academic Press, New York, 1983).

[7]M. V. Vol'kenshtein, Biofizika (Biophysics), Nauka, M., 1981.

[8]I. Prigogine and I. Stengers, La Nouvelle Alliance, Gallimard, Paris, 1979.

[9]P. Glansdorff and I. Prigogine, Thermodynamic Theory of the Structure of Stability and Fluctuations, Interscience, New York, 1971 (Russ. Transl., Mir, M., 1973).

[10]G. Nicolis and I. Prigogine, Self-Organization in Nonequilibrium Systems, Wiley, New York, 1977 (Russ. Transl., Mir, M., 1979).

[11]I. S. Shklovskiĭ, Vselennaya, zhizn', razum (Universe, Life, Mind), Nauka, M., 1976 (Engl. Transl. of earlier edn., I. S. Shklovskiĭ and C. Sagan, Intelligent Life in the Universe, Holden-Day, San Francisco, 1966).

[12]Ya. B. Zel'dovich and I. D. Novikov, Stroenie i évolyutsiya Vselennoĭ (Structure and Evolution of the Universe), Nauka, M., 1975.

[13]I. D. Novikov, Évolyutsiya vselennoĭ, Nauka, M., 1983 (Engl. Transl., Evolution of the Universe, Cambridge Univ. Press, 1983).

[14]J. Silk, The Big Bang: The Creation and Evolution of the Universe, W. H. Freeman, San Francisco, 1980 (Russ. Transl., Mir, M., 1982).

[15]G. Kastler, Vozniknovenie biologicheskoĭ organizatsii (Origin of Biological Organization), Mir, M., 1967.

[16]E. Schrödinger, What is Life? The Physical Aspect of the Living Cell, Cambridge Univ. Press, 1967 (Russ Transl., Atomizdat, M., 1972).

[17]J. B. P. A. de M. de Lamarck, Philosophie Zoologique, Vols. 1-2, Chez Dentu, Paris, 1809 (Engl. Transl., Zoological Philosophy, Hafner, New York, 1963; Russ. Transl., Izd-vo AN SSSR, M., L., 1935, 1937).

[18]E. Mayr, in: Évolyutsiya (Evolution), Mir, M., 1981.

[19]R. Lewontin, ibid.

[20]D. Penny, L. Foulds, and M. Hendy, Nature 297, 197 (1982).

[21]R. Lewontin, Nature 200, 113 (1982).

[22]F. J. Ayala, see Ref. 18.

[23]F. Jacob and E. L. Wollman, Sexuality and the Genetics of Bacteria, Academic Press, New York, 1961 (Russ. Transl., IL, M., 1963).

[24]C. R. Darwin, The Origin of Species (Russ. transl., Collected Works, Vol. 3, Izd-vo AN SSSR, M., 1939).

[25]C. R. Darwin, Change in Animals and Plants upon Domestication (Russ. Transl., Collected Works, Vol. 4, Izd-vo AN SSSR, M., L., 1951).

[26]D. K. Belyaev, Priroda 1979, No. 2, 36.

[27]N. V. Timofeev-Resovskiĭ, N. N. Vorontsov, and A. V. Yablokov, Kratkiĭ ocherk teorii évolyutsii (Brief Sketch of the Theory of Evolution), Nauka, M., 1977.

[28]I. I. Shmal'gauzen, Problemy darvinizma (Problems of Darwinism), Nauka, M., 1969.

[29]V. Grant, Organismic Evolution, W. H. Freeman, San Francisco, 1977 (Russ. Transl., Mir, M., 1980).

[30]L. S. Berg, Trudy po teorii évolyutsii (Studies on the Theory of Evolu-

tion), Nauka, Leningr. otd-nie, 1977.

[31]Zhizn' zhivotnykh (Life of Animals), Vols. 1, 6, Prosveshchenie, M., 1971.

[32]R. C. Lewontin, The Genetic Basis of Evolutionary Change, Columbia Univ. Press, 1974 (Russ. Transl., Mir, M., 1978).

[33]C. A. Villee and V. G. Dethier, Biological Principles and Processes, Saunders, Philadelphia, 1976 (Russ. Transl., Mir, M., 1974).

[34]B. N. Belintsev and M. V. Vol'kenshteĭn, Dokl. Akad. Nauk SSSR 235, 205 (1977).

[35]P. A. P. Moran, The Statistical Processes of Evolutionary Theory, Clarendon Press, Oxford, 1962 (Russ. Transl., Mir, M., 1973).

[36]F. Schlögl, Z. Phys. 248, 446 (1971); 253, 147 (1972).

[37]G. Czajkowski and W. Ebeling, J. Nonequil. Thermod. 2, 1 (1977).

[38]H. Haken, Synergetics, 2nd edn., Springer-Verlag, Berlin, 1978 (Russ. Transl., Mir, M., 1980).

[39]A. N. Severtsov, Glavnye napravleniya évolyutsionnogo protsessa (Principal Directions of the Evolutionary Process), Izd-vo Mosk. un-ta, M., 1967.

[40]J. Avise, Proc. Natl. Acad. Sci. USA 74, 5083 (1977).

[41]J. Cronin, N. Boaz, C. Stringer, and Y. Rak, Nature 292, 113 (1981).

[42]J. Jones, Nature 289, 743 (1981).

[43]R. Lewin, Science 210, 883 (1980).

[44]M. V. Vol'kenshteĭn, Dokl. Akad. Nauk SSSR 263, 722 (1982).

[45]E. K. Tarasov, Khimiya i zhizn', No. 2, 56 (1981).

[46]A. A. Neĭfakh, ibid. No. 2, 40 (1982).

[47]S. Luria and M. Delbrück, Genetics 28, 491 (1943).

[48]M. V. Vol'kenshteĭn, Molekuly i zhizn', Nauka, M., 1965 (Engl. Transl., Molecules and Life, Plenum Press, New York, 1970).

[49]J. Bonner, ed., Evolution and Development, Springer-Verlag, Berlin, 1982.

[50]R. Lewin, Science 214, 42 (1981).

[51]M. Zussman, Biologiya razvitiya (Biology of Development), Mir, M., 1977.

[52]N. Wessels, see Ref. 49, p. 115.

[53]G. Freeman, ibid., p. 155.

[54]L. Wolpert, Sci. American 239, No. 4, 154 (October 1978).

[55]L. Wolpert, see Ref. 49, p. 169.

[56]H. Meinhardt and A. Gierer, J. Theor. Biol. 85, 429 (1980).

[57]A. Gierer, Naturwissenschaften 68, 245 (1981).

[58]A. Turing, Philos. Trans. R. Soc. London 237, 32 (1952).

[59]V. Ebeling, Obrazovanie struktur pri neobratimykh protsessakh (Structure Formation in Irreversible Processes), Mir, M., 1979.

[60]H. Schaller and H. Bodenmüller, Naturwissenschaften 68, 252 (1981).

[61]B. N. Belintsev, Usp. Fiz. Nauk 141, 55 (1983) [Sov. Phys. Usp. 26, 775 (1983)].

[62]T. Kaufman and B. Wakimoto, see Ref. 49, p. 189.

[63]M. Katz, ibid., p. 207.

[64]M. Katz and R. Lasek, Proc. Natl. Acad. Sci. USA 75, 1349 (1978); 78, 397 (1981).

[65]R. Raff and T. Kaufman, Embryos, Genes and Evolution, Macmillan, New York, 1982.

[66]S. Gould, Ontogeny and Phylogeny, Harvard Univ. Press, 1977.

[67]S. Gould, Evolution 32, 29 (1978).

[68]S. Gould and R. Lewontin, Proc. R. Soc. London B 205, 581 (1979).

[69]S. Gould, Paleobiology 6, 119 (1980).

[70]S. Gould, Nat. Hist., No. 2, p. 16; No. 4, p. 19 (1981).

[71]S. Gould, see Ref. 52, p. 333.

[72]H. Jerison, Evolution of the Brain and Intelligence, Academic Press, New York, 1973.

[73]R. Martin, Nature 293, 57 (1981).

[74]R. Lewin, Science 216, 840 (1982).

[75]S. Gould and E. Vrba, Paleobiology 8, 4 (1982).

[76]R. Lewin, Science 216, 1212 (1982).

[77]J. Wolken, Photoprocesses, Photoreceptors and Evolution, Academic Press, New York, 1975.

[78]J. Haldane, The Causes of Evolution, Cornell Univ. Press, 1966.

[79]D. Valentine, see Ref. 18.

[80]V. A. Bol'shakov et al., Dokl. Akad. Nauk SSSR 249, 1462 (1979).

[81]J. D. Watson, Molecular Biology of the Gene, Benjamin, New York, 1965 (Russ. Transl., Mir, M., 1978).

[82]M. V. Vol'kenshteĭn, Molekulyarnaya biofizika, Nauka, M., 1975 (Engl. Transl., Molecular Biophysics, Academic Press, New York, 1977).

[83]R. Dickerson and I. Geis, The Structure and Action of Proteins, Harper and Row, New York, 1969.

[84]R. Dickerson, Sci. American 226, No. 4, 58 (April 1972).

[85]M. Kimura, Nature 217, 624 (1968).

[86]J. King and T. Jukes, Science 164, 788 (1969).

[87]M. Kimura, Sci. American 241, No. 5, 98 (November 1979).

[88]M. Kimura, The Neutral Theory of Molecular Evolution, Cambridge Univ. Press, 1983.

[89]T. Ohta, Nature 246, 96 (1973); 252, 351 (1974).

[90]T. Ohta, in: Molecular Evolution and Polymorphism, ed. M. Kimura, Nat. Inst. of Genetics, Mishima, Japan, 1977, p. 148.

[91]O. T. Solbrig and D. Solbrig, An Introduction to Population Biology and Evolution, Addison Wesley, Reading, Mass., 1979 (Russ Transl., Mir, M., 1982).

[92]M. V. Vol'kenshteĭn, Zh. Obshcheĭ Biol. 42, 690 (1981).

[93]A. Lesk and C. Chothia, J. Mol. Biol. 136, 225 (1980).

[94]R. Dickerson, Sci. American 242, No. 3, 136 (March 1980).

[95]M. V. Vol'kenshteĭn, Genetika, No. 2, 54 (1965); No. 4, 119 (1966); Biochim. Biophys. Acta 119, 421 (1966).

[96]M. V. Vol'kensteĭn, Izv. Akad. Nauk SSSR, Ser. Biol., No. 6, 805 (1971).

[97]O. B. Ptitsyn, Mol. Biologiya 18, 574 (1984).

[98]R. B. Khesin, Nepostoyanstvo genoma (Inconstancy of the Genome), Nauka, M., 1983.

[99]R. Lewin, Science 217, 42 (1982).

[100]D. Brown, Science 211, 667 (1981).

[101]R. Raylor, Nature 286, 837 (1980).

[102]G. Dover, Nature 299, 111 (1982).

[103]R. Lewin, Science 218, 552 (1982).

[104]G. Cooper, ibid., p. 801.

[105]J. Marx, Science 215, 955 (1982).

[106]M. Ptashne, A. Johnson, and C. Pabo, Sci. American 247, No. 5, 128 (November 1982).

[107]I. I. Shmal'gauzen, Kiberneticheskie voprosy biologii (Cybernetic Problems of Biology), Nauka, Sib. otd-nie, Novosibirsk, 1968.

[108]L. Gatlin, Information Theory and Living Systems, Columbia Univ. Press, 1972.

[109]M. V. Vol'kenshteĭn and D. S. Chernavskiĭ, Izv. Akad. Nauk SSSR, Ser. Biol., No. 4, 531 (1979).

[110]M. M. Bongard, Problema uznavaniya, Nauka, M., 1967 (Engl. Transl., Pattern Recognition, Spartan Books, New York, 1970).

[111]R. L. Stratanovich, Teoriya informatsii (Information Theory), Sov. Radio, M., 1975.

[112]R. P. Poplavskiĭ, Termodinamika informatsionnykh protsessov (Thermodynamics of Information Processes), Nauka, M., 1981.

[113]M. V. Vol'kenshteĭn, J. Theor. Biol. 80, 155 (1979).

[114]M. Conrad and M. Volkenstein, ibid. 92, 293 (1981).

[115]P. Saunders and M. Ho., ibid. 63, 375 (1976); 90, 515 (1981).

[116]A. N. Kolmogorov, Probl. peredachi informatsii 1, 3 (1965); 5, 3 (1969).

[117]G. Chaitin, Sci. American 232, No. 5, 47 (May 1975).

Translated by M. V. King