ON THE ORIGIN AND EVOLUTION OF LIVING MACHINES

By HAROLD F. BLUM

> " . . . any analysis of the nature of the evolutionary process must begin somewhere, and it had better begin not too far off and with the condition which can be most probably made out."
>
> —LAWRENCE J. HENDERSON

IF WE wish to contrast the living and the non-living we may compare a living cell with a mixture of chemicals in a test tube. If we wish to find similarities we may do better to compare the living cell with a man-made machine, say an automobile, which may also be contrasted with the contents of the test tube. Clearly we would not try to describe an automobile by grinding up its various parts and subjecting them to chemical analysis, and we would not expect to learn all about the living machine by following, exclusively, a similar attack. It seems hardly necessary to say this and yet we seem at times to go astray in just this direction, whether we are trying to study the nature of viruses, the growth of cancers, the mechanism of genetic inheritance, or, as in the present case, the origin and evolution of life.

A certain parallel may be drawn between the non-living machine and the living machine in that both have evolutionary histories even though these are of different kinds. In tracing the evolution of the non-living machine we might begin a few hundred thousands of years ago when the first usable tool was chipped out of a piece of stone by an ancestor of modern Man. Then trace the story through innumerable steps including the first smelting of metal in Neolithic times, and the development of the effective steam engine less than two centuries ago, to the modern automobile and other complex machines. Viewed in this way it is seen that the evolution of the non-living man-made machine presupposes the evolution of Man himself; and this takes us into the history of living machines, as one of which Man has evolved.

With the story of the non-living machine so entangled with that of the living machine, the definition of a point of origin for the former must be vague or quite arbitrary. And if we try to imagine the various functional components of a living machine emerging from a mixture of chemical compounds—which we think happened sometime within, say, the last four thousand million years—we meet similar difficulty in defining the moment of emergence; perhaps we do better to think of the origin of life as spread over a considerable interval of time, blurred to our view with regard to both the kind and order of the steps that occurred. How the chemical compounds from which the living machine could be constructed, themselves came into being may be regarded as another problem. But

again, separation of this problem from that of the origin of the living machine itself may be quite arbitrary. The analogy between living and non-living machines probably should not be pressed much farther than to point out that neither could be expected to arise spontaneously from a mixture of their component molecules; that is, without some special conditions or events extraneous to the simple chemical mixture itself. It should hardly be necessary to point out that I do not mean by this statement that extraphysical factors or vitalistic concepts need be invoked—the present argument is surely a mechanistic one.

We could find many properties of living machines that do not have their counterparts in non-living ones; but perhaps that which is most striking and most important from the standpoint of origin and evolution is the property of self-replication. Up to now such a property has not been built into any non-living machine. Self-replication of parts, and of the machine as a whole, is of particular importance in the present discussion; for if we are to assume that evolution of living systems has taken place by a mechanism of variation and natural selection, using these terms in the sense of modern Darwinism, this property becomes of paramount importance. The existence of a distinguishable biological species depends upon the accurate replication of a pattern which determines the characteristics of that species. And yet if this pattern were always copied exactly there could be no evolution by natural selection: for this, errors in copying must occur and be replicated in subsequent generations. If by such a copied error—or mutation—a characteristic is conferred that better fits the species to the environment in which it has to exist, the chances of survival of that species are increased, whereas species with disadvantageous mutations tend to be eliminated. This is the process of evolution by natural selection described in oversimplified fashion.

Our knowledge of some aspects of the process of replication is increasing rapidly at the moment—so rapidly that we may at times forget, in our enthusiasm, that the origin of a replicating machine is something different from the copying of such a machine once it exists. The point was emphasized by the late John Von Neumann who, while conceiving a machine that could replicate itself, admitted his inability to imagine a machine that could create itself.[1] The difference between replication and origin was pointed out by Sir William Hardy a good many years earlier (1934) in an essay entitled, "To Remind" (which seems to have reminded few), basing his argument on the difficulties of the origin of a machine that could manufacture one only of two possible optical isomers, as living organisms do.

But to be more specific, let us consider the process of self-replication as we see it in modern living machines. And for the sake of argument let us

[1] Said in his Vanuxem Lectures at Princeton University in 1952.

try to reduce this process to a minimum of functional components that have to do with replication, leaving aside many other intriguing properties of living systems. If we are to give any physical solidity to our ideas of replication it seems necessary to assume some sort of spatial pattern, which we may think of as a template composed of large molecules having specific configurations that provide necessary genetic information for the construction of the individual organism making up the species. We have to think that not only are materials replicated by building against this template but that in some way the template itself is replicated in the course of self-duplication of the machine as a whole, so that the pattern can be passed along from generation to generation. Such replication entails the expenditure of free energy, since assembling the material against the template and taking the replica off cannot both be spontaneous acts; so there must be an energetic, or thermodynamic, component of the machine. And, as we shall see later, the mobilization of free energy in the living cell also entails a kinetic component. Thus it is necessary to think of the replicating machine in terms of no less than three functional components;[2] let us refer to them as spatial, energetic, and kinetic. So in thinking about the origin and evolution of such a machine we must take into account the origin of all three of these components rather than of any one of them alone. It is difficult to conceive how a machine that embodied all three could have come into being as a sudden act; and it would seem more likely that the different components were introduced separately. At any rate, until the complete self-replicating machine had emerged, evolution by natural selection, in the sense in which this word may properly be used, was not possible; and here an error may creep into our thinking about the origin of living systems. For natural selection is sometimes wrongly invoked, directly or tacitly, to explain the origin of things which had to be present before evolution by natural selection could take place, that is, to explain events leading up to the appearance of the self-replicating machine in terms of things that could have happened only after such a machine was already in existence. This incorrect application of the concept of natural selection may lead into the realm of teleology and finalism.

Undoubtedly there was going on before living machines were perfected to the point where natural selection was possible, a process which I like to call "chemical evolution"; and from this evolution resulted many types of compounds that are indispensable components of living machines today. An outstanding example is the amino acids, which,

[2] In an earlier paper (1957) I described the minimum requirement of these three functional components, which I there called "functional properties." It should be pointed out, perhaps, that every reacting system involves, in an analytical sense, spatial (or structural), energetic and kinetic components; and that when the terms are used here with reference to living systems they refer to specific components of the latter systems.

combined in proteins, are found playing basic roles in all living species. Before considering the origin and evolution of the living machines themselves, let us discuss briefly this process of chemical evolution, which may be more nearly compared to what may happen to a mixture of chemical compounds in a test tube.

Chemical Evolution

Let us consider first some thermodynamic and kinetic aspects of chemical reaction in a complex system. It is convenient to represent the free energy changes in a given reaction schematically as in Figure 1, where A represents an *exergonic* or *spontaneous* reaction, that is, one that will

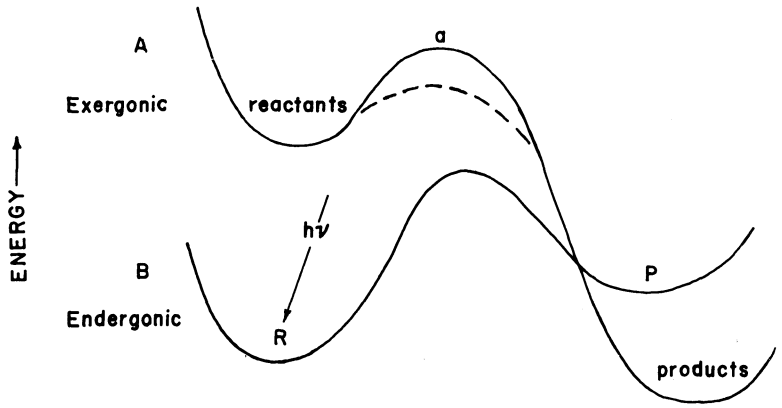

FIG. 1. Diagram of free energy relationships in an exergonic reaction, *A;* which might drive the endergonic reaction represented at *B* (see text).

go by itself. In such a reaction free energy decreases, as is indicated by the reactants having a higher position on the diagram than the products. Both reactants and products are indicated as lying in depressions, separated by a barrier that represents the energy of activation.[3] We think of the reactant molecules as jumping about in their basin—now and then one of them jumps high enough, that is, gains enough energy, to pass over the barrier and fall into the product basin. The chances of getting back into the reactant basin are less because of the difference in free energy level, so products increase and reactants diminish, until equilibrium is ultimately established. According to this picture it is the height of the barrier, that is, the energy of activation, that determines the rate at which the reaction will go—the higher the barrier the less molecules pass over it in unit time. The free energy and energy of activation are not proportionally related, so rate and direction of reac-

[3] For convenience, the term *free energy* will be used to describe the free energy of reaction; *energy* of *activation* to describe the free energy of activation. Both terms may be used loosely at times.

tion are essentially independent. The free energy determines the direction and extent to which the reaction can go, and the maximum amount of useful work that can be obtained when it goes; but does not tell us what the rate will be. For example, the oxidation of glucose goes with a high free energy change, but very slowly at ordinary temperatures if left to itself. There are various ways to change the rate of reaction without altering its direction. If the temperature of the system is raised, the average energy of the molecules is increased with the result that they more frequently attain the energy of activation, and so the speed of movement toward the product state is increased. Another way to speed up a reaction is by catalysis, which may be brought about in a variety of ways, say by introducing a surface on which the molecules can be adsorbed, or by means of an appropriate enzyme. Without attempting to explain mechanisms of catalysis we may indicate its effect as a lowering of the energy of activation, as suggested by the dotted line in Figure 1. The result is that at a given temperature more molecules reach this critical energy within a given time, and hence the rate of the reaction is increased.[4]

The reaction represented at B in Figure 1 is *endergonic*, that is, the products P end up at a higher energy level than the reactants R, and in order for this to happen energy must be put in. This may be accomplished, at least conceptually, by coupling with an exergonic reaction such as A in the diagram; but, as indicated in the figure, the whole process must end up with a loss of free energy if the second law of thermodynamics is to be satisfied. Another way to drive a reaction "uphill" is to add energy directly to the reactant molecules, say, by having them capture quanta of radiant energy ($h\nu$), if the quantum can supply enough energy to get the molecule over the energy of activation[5] barrier from the lower level. Both these ways of driving reactions uphill are of paramount importance to living systems. Coupled reactions are basically concerned in the utilization of the fuel supply from which the organisms obtain their free energy for a multiplicity of syntheses, accomplishment of mechanical work, the maintenance of structure, etc. By a photochemical reaction (photosynthesis, carried out by plants) living machines gain their supply of fuel.

Perhaps I have taken too much space for this elementary, oversimpli-

[4] An elementary discussion of these energy relationships which may be useful to some readers is given in Blum, 1962.

[5] In biochemistry the term "activation" may sometimes be used to describe a step by which free energy is introduced, for example in the formation of the peptide linkage. In this case the term seems to describe an endergonic process, i.e., a thermodynamic change which has to do with direction of reaction; whereas, as used here, and generally in chemical kinetics, the term activation energy describes something that determines the rate of the reaction without affecting its direction. The terms "activity" and "activation" are given a number of specific meanings in different domains of science, so one must make sure as to the way they are being used in a particular context.

fied discussion, but it seems necessary to have the essential difference between the *rate* of a reaction and its *direction* always in mind if we are to gain an idea of what happened once upon a time under the complicated conditions prevailing at the surface of our primitive planet and to compare that situation with what goes on in living systems today—if we do not oversimplify we become discouraged at the very outset.

Things that might happen in a complex mixture are diagrammed in Figure 2. Three reaction pathways are indicated, starting from the reactants at A. The series of reaction steps going from A through B,

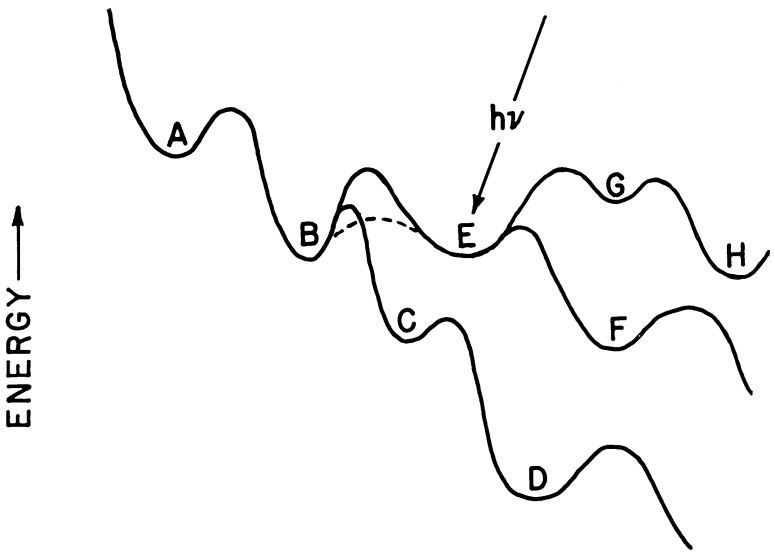

FIG. 2. Diagram to illustrate free energy relationships of three hypothetical reaction pathways in a complex mixture of molecular species (see text).

C, and D, is thermodynamically the most probable of those represented because it goes with the greatest total loss of free energy. The pathway leading from B through E and F, is also thermodynamically possible since the latter both lie at lower free energy levels than B, but this course is opposed by the high energy of activation that separates B from E, which is greater than that separating B from C. Under the conditions, C would be formed faster than E, and the latter might never accumulate in important quantity. But suppose that in some way a catalyst was introduced which lowered the energy of activation barrier between B and E, as indicated by the broken line, to the extent that E formed faster than C. The course of the reaction would then be altered; E could now react to form F and from then on a pathway would be followed which was different from that most probable before the catalyst was introduced. Under appropriate conditions the E molecules might

capture quanta of radiant energy, and so be raised to energy levels high enough for G to be formed; G could then go spontaneously to H, opening up another pathway of reactions. Electrical discharge might accomplish the same thing, and the diagram might be further complicated by introducing coupled reactions, autocatalysis, and other factors. Needless to say, although it could not be easily shown in the diagram, the direction of reaction would be influenced by the proportions of the various reactants and products present; that is, mass action is a factor in the free energy relationships.

Out of such a system could have come—obviously did come—a multiplicity of chemical species, setting the stage for the emergence of life. I would emphasize the basic importance in this regard of the operative independence of thermodynamic and kinetic factors—of direction and magnitude of free energy change, as contrasted to rate of reaction—in this process of chemical evolution. If one could imagine that only the former prevailed, the result would be more predictable but ever so much more monotonous; lacking the flexibility introduced by kinetic factors the end result would be a dead level at which all the reactions most probable thermodynamically had been accomplished, with no further pathway to be followed.[6] The possibility of modifying rates by catalysis and of changing the free energy relationships through factors extraneous to the immediate system, radiant energy, electrical discharge, etc., introduces an aspect of "choice" into the picture, permitting certain reaction pathways to be "selected" rather than others.[7] Such choice should have had its effect not only in chemical evolution but upon the biological evolution that followed. For living systems could only be built from the material at hand, and these materials were the products of the chemical evolution that preceded the advent of life.

We see that for chemical evolution to occur, both a thermodynamic and a kinetic component are necessary; but no spatial component in the sense of a replicated pattern is required, and no machinery for replication. This lack would seem to establish a sharp distinction between chemical evolution in a non-living world, and evolution by natural selection in a world of living machines. The emergence of the latter thus presents a crucial problem.

During the last decade there has been resurgence of interest in problems of the origin of life. This was spurred by the dramatic experiments of Miller in 1953, which stemmed from Urey's ideas regarding the primitive atmosphere; both pay tribute to Oparin, whose book, "The Origin of Life," was first published in 1937 (revised edition 1957). That a First

[6] This was discussed by the author some years ago (1935).

[7] In using the terms "choice" and "selected" I do not, of course, imply extraphysical interference, but only that chance events outside our cognizance—and perhaps only within that of Laplace's demon—have determined the pathway to be followed.

International Congress on the Origin of Life was held in Moscow in 1957 testifies to this revived interest in an old problem. The proceedings of that Congress (1959) include papers from various parts of the world and from different scientific disciplines. As might be expected, the points of view represented in this volume are diverse, and points of agreement few—a healthy condition in a field where evidence is scanty on the whole and speculation essential. Under these circumstances, criticism should be guarded, and I should not venture to offer any that would be specific in nature. But I would submit that, in these papers of the Moscow symposium, the emphasis is not on the origin of life, but on the origin of an environment that would provide the materials from which living machines of the kind we know could be built, with relatively little attention given to the problem of origin of the living machine itself. The greater part of these papers deals with what I should include in chemical evolution. There seems to be tacit at various points the idea that once there was present a mixture of the component molecules, life must spontaneously arise and evolve. This idea seems also to tinge much of the thinking about life on other worlds which has become a popular subject for speculation in this "Space Age." Difficulties with this point of view become apparent, however, when we examine further into the problems of replication of living machines.

Replication of Living Systems

Each time a cell divides its essential parts have to be replicated; and since each of the resultant cells has the potentiality of dividing, the pattern for replication of these parts must be one of the parts that is replicated. In biology the term template is now generally associated with the patterns for replication; analogy is implied to a device for ensuring spatial arrangements. A common kind of template in mechanics is a thin plate with holes at appropriate places to establish the position of screws or bolts, a paper dress pattern serves its purpose in a similar way. *Biological templates* that fulfill the function of determining spatial relationships are to be pictured as consisting of molecules composed of atoms held together in quite exact spatial arrangement. They need to be thought of as spatio-energetic patterns, in the sense that, being held together by inter-atomic bonds (which represent states of minimum energy), an energetic pattern is also involved in their arrangement. In replication against such a template, bonds must also be temporarily formed between atoms of the template and those of the molecular units replicated against it. Thus, it seems necessary to assume that in replication against a template inter-atomic bonds have to be formed and broken, and that replication must, thus, entail a mechanism for doing this.

The templates in modern living systems may be regarded as long polymers made up of large numbers of monomer units, similar but not

all identical. The pattern for different biological species would seem to reside in specific arrangements of the monomers in the polymer template. This pattern must be very stable, in a biological sense, to insure the stability of the species, yet be subject to occasional minor local alterations, which comprise the mutations necessary for evolution by natural selection.[8] Let us consider the energetic relationships concerned in replication of such a polymer against a corresponding polymer which acts as template, thinking for the moment in terms of models that are not directly descriptive of replication in living systems.

We may begin by assuming the pre-existence of a polymer template against which we are going to assemble monomer units to form another polymer that will be a replica of the original. For our first example let us think of the monomers becoming attached to the polymer by interatomic bonds, the forming of which is an exergonic reaction, and that bonds also form between the monomer units, these reactions also being exergonic. We now have the replica polymer formed in place against the template polymer; the next problem is to take the replica off without disrupting it. That is, we must break the bonds between the two polymers without breaking those between the monomers. In whatever way this is to be done it would seem that energy must be introduced in breaking bonds, for it is difficult to imagine the free energy relationships to favor the forming of the replica on the template and at the same time favor its removal. In any event, free energy would be needed to reestablish the conditions necessary to begin another replication. So there is entailed an energy cycle having two phases, one exergonic, one endergonic; the replicating machine expending free energy in one or the other phase of the cycle, if not in both.

There are other aspects that must be included in any successful model and these I want to illustrate by constructing another one, again entirely fictitious and not supposed to represent closely what goes on in the living system. This model I have tried to diagram in Figure 3; where is represented on the left-hand side at A, a template polymer, the zig-zag contour indicating its spatial configuration. To the right of the template are represented three monomers M_1, M_2, and M_3, which have complementary shapes that permit them to be fitted into the specific positions on the template polymer. The solid arrows behind the monomers on the right indicate some kind of forces "pushing" them into position against the template polymer. In the model previously described these forces could be thought of as the result of the negative free energy of an exergonic reaction, but, in the present model, let us imagine that the attachment of the monomer units to the polymer is endergonic so that free energy must be expended in getting them into place on the template. Once in

[8] Neglected, for simplicity, are the various rearrangements of the templates, although this may be of great importance in evolution.

place they need to be held there until the replica is completed; this might be accomplished by energy of activation, as is represented diagrammatically at b_1, b_2, b_3 in B of Figure 3. This energy of activation has of course to have been supplied, together with the required free energy, in getting the monomers placed against the polymer template. The removal of the replica from the template now becomes an easy matter, since it is only necessary to introduce a proper catalyst to lower the energy of activation

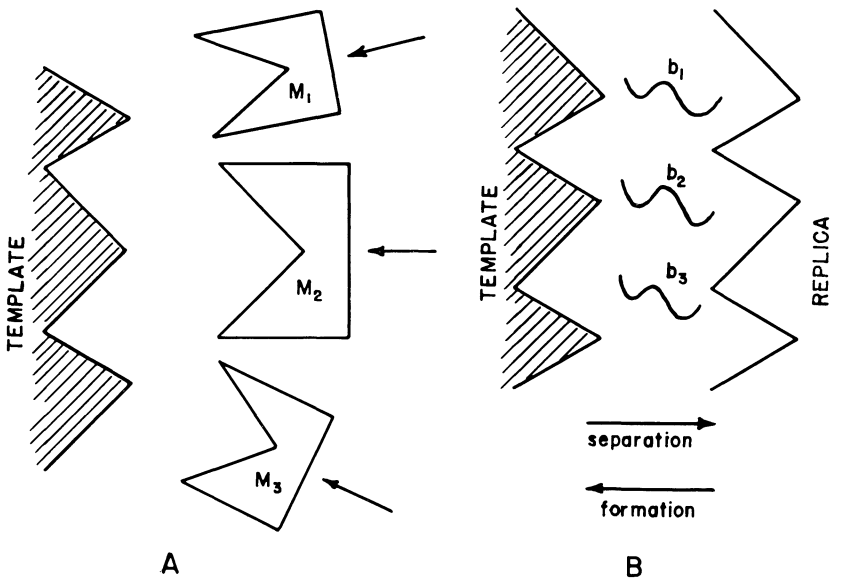

FIG. 3. Models to illustrate problems of replication against a template (see text).

and the replica comes off. We now have our replica separated from the template.[9] The scheme for removing the replica from the template seems simple enough since only an exergonic reaction is involved; but note that in introducing the catalyst, free energy has had to be expended somewhere in the system, and, of course, we do not forget that energy has been used in putting the monomers in position against the template in the first place. No doubt I could have used a model which would have been more closely analogous to the mechanism of replication in living systems; but I might have run the risk of taking it too seriously, and what I have wanted to point out is that these, or any other models we may imagine, must involve both endergonic and exergonic phases, the over-all process being a cycle.

It is time now to think about the real living machine, but here again I would like to follow a schematic approach. Let us consider first how

[9] We note that the replica is a mirror image of the template from which it comes; but let us not be concerned here with this aspect of spatial relationships, since we have enough to do to resolve the energetic and kinetic problems confronting us.

the free energy may be supplied, using Figure 4 to indicate diagrammatically the situation in modern living systems. The figure schematizes, loosely, the energetic relationships in metabolism of cells. A supply of "energy-rich" compounds is required which is made available by photosynthesis, represented on the left of the diagram, where is indicated the combination of CO_2 and H_2O into energy-rich compounds, symbolized by (CH_2O), with O_2 a product; the energy for this endergonic reaction is supplied by sunlight symbolized by the quantum, $h\nu$. Although photosynthesis may take place at a distance from the particular replicating cell (in every animal cell, for example) it has to be included in a complete energy balance sheet since it is the ultimate source of energy for all living systems; but for the present we are only concerned with the use of the fuel after it is supplied to the cell. In Figure 4 the energy-rich carbon

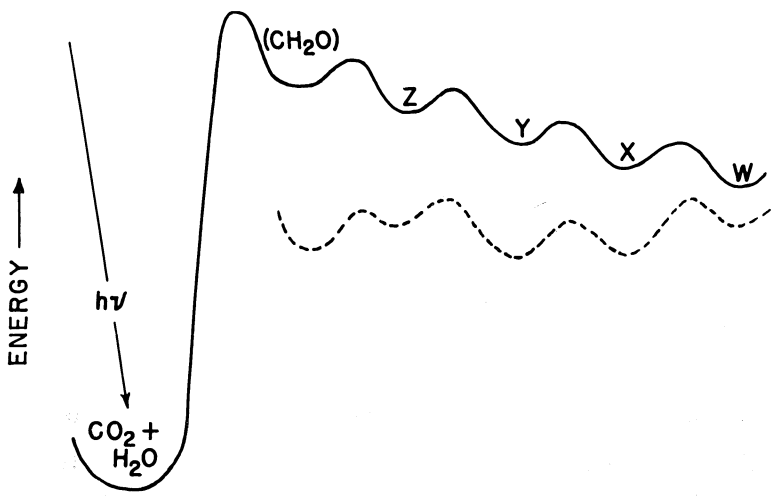

FIG. 4. Diagram to illustrate energy relationships in the living machine (see text).

compounds are indicated as entering into a variety of reactions taking place in a step-wise fashion (Z, Y, etc.); each step entails a decrease in free energy, and also has a characteristic energy of activation. There are specific catalysts—enzyme systems—concerned in the various steps, and these make possible the utilization of the high free energy of such a reaction, as for example, the combustion of glucose (688 kg. cals. per mol.), in a series of small modulated steps (of around 10 kg. cals. per mol.). From this downhill process, the cell is able to tap off small amounts of free energy which it employs in various ways, including the synthesis of essential compounds, and the work of replication.

For purposes of illustration the three minimum components for replication—spatial, kinetic, and thermodynamic—may be associated with specific kinds of compounds in living systems. The kinetic function is

associated with protein, since an enzyme constitutes at least a part of every catalytic system in living cells; and the spatial component with nucleic acid, DNA (see page 487) being at least a major component of the master templates of cells. The thermodynamic component includes energy-rich compounds, a wide variety of which may be used. Specific compounds serve in the transfer of small quantities of free energy, represented by the small steps in Figure 4; including members of the adenylic acid system, adenosine mono-, di-, and triphosphate (generally referred to as AMP, ADP, and ATP, respectively), transfer of free energy being associated with transfer of "energy-rich" phosphate groups.

The difficulty is that, although such a classification as the above may be useful for illustrative and analytical purposes, when we examine our categories in more detail, and particularly when we try to relate them to the machinery of replication, they become inextricably tangled. This does not mean, of course, that we should not attempt to break down the living, replicating system into its component parts for study—this is an essential procedure. But we should recognize, always, that we cannot perform this analytical separation into parts without destroying the machine as a whole. This is as true if we carry out the analysis at a theoretical level as if we do so experimentally.

Thus, the separation of replication into three minimum components, which I make here, can only be regarded as an analytical tool; useful within limits, but not describing the integrated machine. But having separated these components for this purpose and associated them with certain kinds of compounds, let us examine the formation and constitution of the latter in a little more detail. The essential structure of the protein is the polypeptide chain, which is formed by joining amino acids together to form a long polymer. As is indicated in Figure 5, the addition of each amino acid involves the removal of one molecule of water; and since the cell is an aqueous medium, it would be expected that this would constitute an endergonic reaction. It is found indeed that the formation of dipeptides by the joining of two amino acids involves positive free energies averaging around 2 to 5 kilogram calories per mole (Borsook, and Dubnoff, 1940). Moreover, we know that the proteins may be hydrolyzed to their constituent amino acids catalytically by appropriate enzymes. Thus, it seems that the formation of proteins in the living cell must be an endergonic process requiring that free energy be expended somewhere in the system. Although the exact process is not understood, it seems pretty well agreed that this expenditure is to be associated with the transfer of an energy-rich phosphate group, probably involving the adenylic acid system. Proteins are not simply long polypeptide chains however, but are more complex in structure and no doubt their formation involves more complicated thermodynamic relationships (e.g., Linderstrøm-Lang, 1952). Hydrogen bonds can form between oxygen and ni-

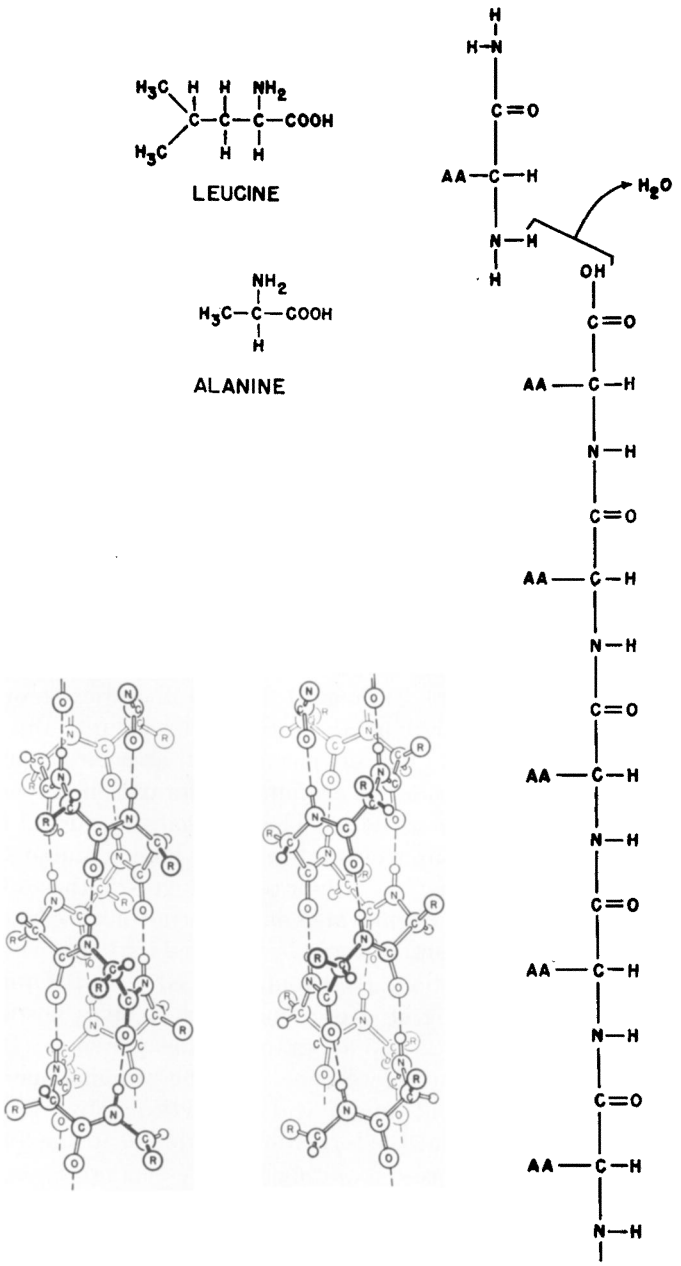

FIG. 5. Upper left, two amino acids. Right, a polypeptide chain; *AA*, represents an amino acid residue. Lower left, Models of polypeptide chains in proteins (from Pauling, The Nature of the Chemical Bond, 3rd Ed., 1960, Cornell University Press; reproduced with the permission of the publisher); showing helical coiling (*R*, represents amino acid residue). The two helices are right- and left-handed forms, both constructed from laevo amino acids.

trogen atoms of the amino acids, giving the polypeptide a three-dimensional configuration, of which the helix illustrated in Figure 5 may be one of the most common. In addition, there are side linkages between the amino acids that hold the polypeptide chains in spatial configurations which probably have much to do with the specific character of the different proteins. So it might be difficult to calculate the free energies for formation of a protein; although, for reasons given above, it seems clear that the over-all process of forming a protein against a template that will give it a specific configuration with regard to the order and arrangement of the various amino acids, is an endergonic process. At any rate, from what has been learned from the above models for replication it is necessary to assume that the formation of proteins *in vivo* is a process in which free energy has to be *expended.* There is no thermodynamic objection to this so long as the machinery is present for doing the necessary work. We see at once, however, that forming the first proteins from a mixture of chemical compounds—sometime, somewhere—on the surface of the earth is a problem of another order; but this is getting ahead of our story.

The nucleic acids like the proteins may be regarded as long polymers, in which many nucleotides are joined together to form a polynucleotide. Each nucleotide is composed of a pyrimidine or purine base, which gives it its specific character, together with a five-carbon sugar and a single phosphate group. There are two kinds of nucleic acid, ribose nucleic acid or RNA and desoxyribose nucleic acid or DNA; these are distinguished by the sugar, ribose or desoxyribose, respectively, which is found in the nucleotides. Biologically, the two types of nucleic acid play quite different roles. Reference to Figure 6 shows that the joining together of the nucleotides involves the removal of one molecule of water per nucleotide. A parallel is to be noted between nucleic acids and proteins in this respect; the joining of the amino acids to form the latter being also accompanied by removal of water. Similarly we might expect that the formation of nucleic acid from nucleotides, in an aqueous medium, would be endergonic, and would require the intervention of machinery to furnish the necessary free energy. Again, the problem poses itself as to how these compounds, which are essential parts of the living machine got formed in the first place in a non-living milieu. To be sure, it has been shown that polynucleotide chains can be formed from di- and tri-phosphate nucleotides in aqueous medium, in the presence of appropriate enzymes. But presumably the loss of the phosphate groups from the di- or triphosphate nucleotides in forming mono-phosphate nucleotide polymers and phosphoric acids goes with decrease in free energy, the over-all process being exergonic. Whatever relationship these *in vitro* reactions have to the synthesis of nucleic acids in living systems they do not seem too likely under conditions

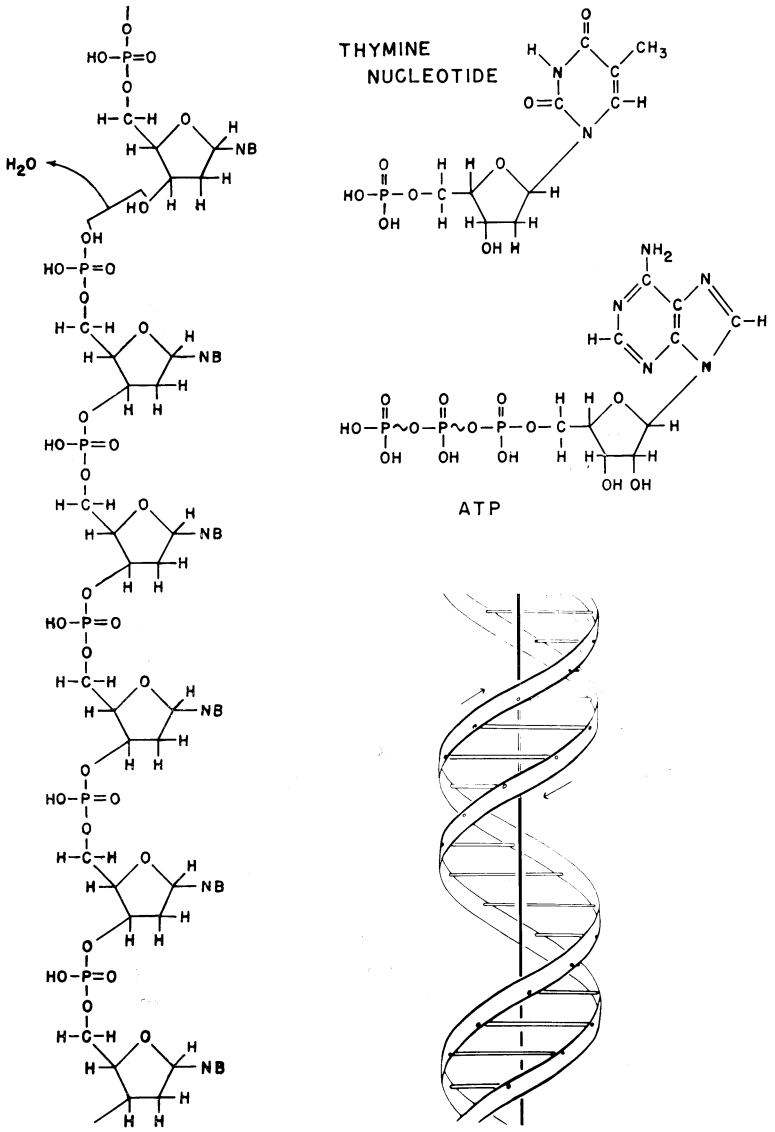

FIG. 6. Upper right, two nucleotides, thymine nucleotide and ATP. Left, a polynucleotide chain of desoxyribose nucleotides; NB, indicates the positions of the purine or pyrimidine bases. Lower right, Watson and Crick's model for DNA.

extant when life originated, unless appropriate catalysts were also present.

As in the case of the proteins, the nucleic acids, are not to be regarded simply as straight polymer chains. In DNA the polynucleotides are arranged in helical fashion, as in the double helix model of Watson and

Crick shown in Figure 6. This DNA structure is a very compact one which takes advantage of the complementary shapes of the purine and pyrimidine bases, permitting the formation of hydrogen bonds between them. The compact arrangement of DNA would seem to favor the stability that must characterize the master templates in living cells—which is the basis of stability of species—and this appears to be a major role of these compounds. The spatial arrangement of RNA, whose essential role seems to be played in the synthesis of proteins, is less well understood; it is apparently less compact.

We come now to those compounds associated directly with the thermodynamic component of replication. The source of energy supply consists of a variety of energy-rich carbon compounds, although the reaction steps follow similar channels. Interesting to us in the present argument is the adenylic acid system which, as has been pointed out, takes part in the transfer of free energy in small amounts, because AMP, ADP, ATP are respectively mono-, di-, and tri-nucleotides as is seen from the structure of the latter shown in Figure 6. The two terminal phosphate groups in ATP and the terminal group in ADP are "energy-rich" groups, which is a way of saying that in transfer of one of these phosphate groups to some other compound in the system a certain amount of free energy is transferred; let us say around 10 kilogram calories per mole. From what has been said above about the *in vitro* formation of poly-nucleotides it would seem probable that the removal of such terminal phosphate groups provides the energy for joining the nucleotides into nucleic acids, and it is also thought that energy from this source provides that which is necessary for joining the amino acids into polypeptides. This may offer an example of inter-relation between the three components of replication which I have chosen to separate for analytical purposes—clearly these three components could not be taken out of the machine itself and still have replication.

Origin and Evolution

So far as we know—and exploration has been extensive—proteins and nucleic acids serve in like roles in all the living organisms that exist today; and it seems most improbable, on the basis of evolutionary reasoning, that any other kinds of compounds have played these roles during at least the 500 million years of the continuous fossil record. Indeed, when we witness the recurrence of a structure such as that of the nucleotides in important roles in living systems, or when we consider the wide distribution and roles of tetra-pyrrol compounds, it becomes pretty clear that living systems have been constructed out of similar kinds of chemical compounds. It was brought into particularly clear focus by Florkin in his little book *Evolution Biochimique* (1944) that we may trace an evolutionary pattern of biochemical compounds which corresponds

in its implications to our tracing of the evolution of morphological aspects of the species of living organisms. There is a basic pattern here—the only question is, perhaps, how far back does it go? From the evolutionary point of view we might be justified in asking whether compounds such as proteins and nucleic acids, for example, have played their respective roles since the origin of the first living organisms, or have evolved subsequently from something else that went before. It seems necessary to assume that these compounds already occupied their present roles 500 million years ago at the beginning of the Cambrian, but we must not forget that there was a prior period, perhaps several times as long, during which biological evolution was going on. The question is certainly useful in stimulating thought, and both possibilities might have to be included in the complete picture. I think, however, that at least most biochemists and others on the physical side, will lean toward the first view, which is certainly useful as a working hypothesis.

In any case, it seems necessary to assume that a variety of chemical compounds appeared as a result of chemical evolution; and that from the resultant environment the first living organisms were produced. However the first living machine was built it would have had to be constructed from those materials that were available; and it would seem reasonable to think that the pattern of replication has not changed essentially, so that the materials found in living organisms today reflect the structures of the original compounds, even after millions of years of evolution. Miller's experiments (1953) have given strong support to this idea. In these he simulated a primitive atmosphere with a mixture of water vapor, ammonia, methane, and hydrogen, and passed through this an electric spark; among other things some amino acids were formed (see also Miller and Urey, 1959). Abelson (1957) isolated amino acids from fossil material going back a good many million years and showed that these compounds might last a very long time on the earth's surface, provided no life was present to devour and incorporate them into its own metabolism. Abelson also repeated Miller's experiments with some variation of conditions and it now seems clear that, even allowing some latitude in our ideas of what constituted the primitive atmosphere of the earth, electric discharge or ultraviolet light could have produced amino acids, among a variety of other compounds. This seems an encouraging step toward an understanding of the origin of life, and certainly Miller's experiments have stimulated a great deal of interest in the study of the probable early environment from which living systems emerged.

But even though amino acids were formed in considerable quantity and collected in water on the surface of our planet, the forming of proteins from them would still present a problem, since, as we have seen already, the joining of the amino acids into polypeptides in aqueous

medium is an endergonic process. The formation of polypeptides from amino acids should be favored by absence of water, however, and it is possible to produce them in the laboratory under anhydrous conditions. Sidney Fox thinks that the formation of polypeptides under conditions of heat and dryness represents an early step in the origin of life and has had considerable success in forming protein-like polypeptides *in vitro* (see Fox, 1960).

I am going to introduce another model for the first replication of long polypeptides, that would seem to fit with Fox's ideas. I doubt very much that this model describes with any exactitude the way life originated on the earth, but I find it useful in distinguishing some of the problems that need to be faced when one tries to extrapolate back into the period when the transition from non-living to living was taking place. Let us suppose that there existed on the surface of the earth, at some point in that uncertain time, a puddle containing a mixture of amino acids. These could have been previously formed in the primitive atmosphere. And let us suppose that the sun's rays heated this pool, driving off water to a point where formation of polypeptides was favored. With rotation of the earth the puddle would start to cool and the overlying air as well, so that water would be returned to the pool from the now unsaturated atmosphere. This would tend toward breaking up of the polymers into their component monomers. With successive diurnal changes a cycle might have been established in which formation of the polymers and dispersion into their component parts tended to alternate. But there should also have been a tendency for the polymers formed during the hot phase to persist during the cool phase because of the energy of activation barrier which would tend to keep the monomers from separating. In this puddle, stirred by alternate heating and cooling, there should have been a good deal of shuffling about of molecules and so the amino acid monomers making up the polymers might come into close geometrical relationships that favored the formation of hydrogen bonds. As a result of such a cycle many times repeated, some rather stable long polypeptides might be expected to result. A supply of amino acids should always have been present, since there would be a tendency for the polymers, particularly the less stable ones, to break down into their component parts. We may imagine that some of these free amino acids would tend to line up along the persisting polymers according to their complementary patterns, and become joined together during the hot phase so as to form other polymer chains which were more or less replicas of the one to which they were attached; in other words, some of the polypeptide chains might have acted as templates upon which other polypeptide chains could be replicated. In the beginning, the formation of polypeptide chains might have been favored by solid particles in the puddle (e.g., Bernal (1951)), but sooner or later some replicable template had to emerge—this is a

crucial aspect of the problem. There would in any case be the problem of separating replica and template without breaking them up into their component amino acids, so we have to imagine some mechanism for this; let us suggest that this was in some way accomplished by change in ionic concentration with the hot and cool phases of the cycle.

We have now imagined a mechanism for the replication of the first polypeptides—it is a pretty vague one and the imagination has been stretched to include a number of things, so I am sure no one is going to accept this as a picture of what really happened. But it suggests that many factors have to be imagined, even when we try to reduce the number to a minimum, in order to account for the basic kind of replicating machine that could have evolved by natural selection into the vast array of living species that surrounds us. I am not, therefore, going to expand upon either the virtues or the faults of this particular model. The reader may reconstruct it to suit himself. He might for example introduce a photochemical cycle instead of the thermal one I suggest, though I think greater complications might be encountered that way. If anyone objects to my assumption that polypeptides may act as templates whereas nucleic acids seem to play the role in living cells, I might point out that the same sort of cycle could serve for the replication of nucleic acids, except that it is rather difficult to figure out how the nucleotides got into the puddle in the first place whereas it seems easy to put amino acids there. I suppose one could imagine some outside supply of energy other than sunlight, but the latter seems to me the most plausible, cyclic supply to start with. Machinery for using the free energy of chemical reaction, and a photosynthetic mechanism for supplying energy-rich carbon compounds, had ultimately to be evolved; but these need not have emerged before replication. No matter in what order we introduce these factors, a cyclic, energetic process—though not necessarily one having, like sunlight, a regular rhythm—is basic to replication and hence to natural selection. If one wishes to imagine that a different cyclic process preceded and evolved into replication as we know it in living systems, he must find one that did not simply *repeat* itself but which *replicated* itself, since this was necessary if evolution by natural selection were to follow. I can think of no cycle that is self-replicating, in this sense, outside the living world.

There is another aspect of living organisms that many have found difficult to account for in terms of origin, the ability to produce one type of mirror image optical isomer to the virtual exclusion of the other. Two such isomers, for example, laevo and dextro lactic acid, have exactly the same configuration except that one is a mirror image of the other. There are the same number and kinds of bonds between the atoms in the two cases and we have to assume that the same amount of information would be required to describe them, that is, that they have the same entropy; thus they are thermodynamically, and hence chemically, in-

distinguishable. Yet living systems are able to manufacture one of the two mirror images and not the other, and since we cannot explain this phenomenon in thermodynamic or chemical terms it seems necessary to explain it in terms of a spatial pattern. That is, we may imagine a template which contains one of the two possible configurations and against which only one of two possible mirror images can, hence, be replicated; this is a very strong argument in itself for the existence of spatial templates in living systems.

Although there are many instances of the existence of only one mirror image isomer in living systems, one which has received a great deal of interest has to do with the amino acids and proteins. The proteins are made up of amino acids of only the laevo type. There are actually dextro amino acids to be found in living organisms, and there are even enzymes which can break down any peptides that might be formed from them. So one might imagine that living systems manufacture both laevo and dextro amino acids, but that the dextro form never comes to be polymerized into proteins. Such a mechanism would demand, however, that the enzyme that took care of the destruction of peptides of dextro amino acids would itself have to have some sort of specific action which could only be explained in terms of its having one of two possible optical isomeric patterns in its constitution. How are we going to explain the origin of polypeptides composed of only laevo amino acids? Or, to make the argument more general, how explain the origin of templates upon which only one of two optical isomers will be formed, which of course supposes that the template itself presents one of two possible isomer patterns?

A variety of hypotheses has been proposed; but these fall for the most part into two general categories. The first assumes some environmental factor which is biased toward the formation of one of the two mirror image forms. The influence of circularly polarized light has been proposed since some photochemical reactions can be biased toward one or the other mirror image form by the action of this agent; but the effect seems relatively slight, and in any case one has to make the assumption that there was, in the environment at the time living systems emerged, a powerful flux of circularly polarized light and this seems difficult to account for. It has also been suggested that the composition of the first polypeptides was influenced by the presence of substances, for example, quartz crystals which, being of one mirror image form, could serve as patterns. Such explanations entail, however, the assumption that the formation of the pattern itself was biased, since one mirror image form is as probable as the other, and thus such an explanation only removes the problem one step. Another form of hypothesis entails some kind of highly improbable event that happened only once. But a simple estimate regarding polypeptides composed of monomers of one mirror image form

should give us pause to consider the rarity of such an event (e.g., see Blum (1957)). Moreover, there seems tacit in such arguments the provision of a machine that would insure the replication of the pattern arising from such an unusual event.

Natural selection has also been invoked—as Wald (1957) puts it, one of the two isomeric forms may have "won in the fight." But starting from the expected fifty-fifty mixture of dextro and laevo amino acids, we might predict the outcome of a fight for combination into peptides in a non-living system to be something like that of the gingham dog and the calico cat. If natural selection is to be invoked, a plausible mechanism is needed, in which the aspect selected is other than mere "right" or "left" handedness. If, as seems likely from their spatial relationships, templates formed from only one of the two possible mirror image amino acids are the most stable, then, given the machinery for replication, natural selection for stability of template pattern (which would correspond to stability of the species) could have taken place. Or again, the single isomer form of polymer might for structural reasons provide more effective or specific catalysis and be selected for this reason. At first consideration, however, it would seem that the most that could be expected from selection on either count would be that polypeptides composed exclusively of either dextro or laevo amino acids would tend to be replicated rather than polypeptides composed of a mixture of the two; but that there would be no selection of "laevo" as against "dextro" polypeptides. Let us imagine a more gradual selection toward "purity" of isomeric form starting, say, from polypeptides composed of fifty-fifty dextro and laevo amino acids. If, by chance, a polypeptide was formed and replicated which contained a somewhat greater proportion of laevo amino acid residues, and hence was more stable or more effective catalytically, it should tend to be selected. Then, subsequent chance alteration of the template resulting in a still greater proportion of laevo amino acids could add further advantage; and so, by a serial improvement in function resulting from an increase in proportion of laevo amino acids, the condition of a polypeptide composed 100% of laevo forms might have been reached. Thus, a not too improbable event followed by a series of other not too improbable events could have led to what seems today a highly improbable condition, that is, the production by living systems of polypeptides composed exclusively of laevo amino acids. Such an explanation postulates the existence of machinery for replication. The selection for isomeric purity of polypeptides might have begun very early, say, under conditions such as replication in the alternately heated and cooled puddle that was pictured above, or relatively late in evolutionary history, though surely before the beginning of the Cambrian. But if we are to invoke natural selection at any time, in any way, we must postulate some kind of replicating machine.

Taking these various aspects of the problem into the picture, it seems that the origin of a kind of self-replicating machine that could have evolved into the present array of living species must have involved more than a mixture of molecular species that could compose such a machine. The origin and evolution of essential molecular species by chemical evolution is in itself a fascinating subject but the problem does not end there. More difficult is the subsequent, or possibly concurrent and inseparable, problem of the origin of the machinery that makes possible the replication of given molecular patterns which is, in a basic sense, the living organism.

"Living Molecules" and "Naked Genes"

The use of terms in unusual context can be very effective in scientific communication where analogy is implied or where purposes of emphasis are served. But there is always the danger that such terms may catch the imagination too well, and come to convey ideas or meanings that were not originally intended. This has happened, I think, with the two expressions in the above subtitle. The term "living molecules" was, I believe, introduced to describe viruses when the first of these was crystalized and defined in terms such as one would apply to molecules in the non-living world. There would be no harm in this except that the idea has become quite generally fixed in the scientific as well as in the popular mind that the viruses constitute complete living machines. Allowing a bit of oversimplification the picture is something as follows: The virus consists of a nucleic acid or nucleoprotein component surrounded by a protein jacket. The latter probably serves in forwarding the penetration of the virus into the host cell, and is left behind when the nucleoprotein part enters. Having penetrated the cell, the nucleoprotein part now furnishes a pattern or template for replication by the cell. The greater part of the cell substance may be used up in the manufacture of virus particles, including the protein sheath, with resultant death of the host cell and release of the virus particles. These new virus particles may now infect other host cells and the cycle be repeated. What is to be noted in the present connection is that the virus particle is not a self-replicating machine but depends for its replication upon the metabolism of the host cell. In other words, the host cell is always a part of the machine which replicates the virus particle, the latter not constituting a complete living unit, since the true replicating machine is the cell-virus system. In this system the virus plays essentially the part of a template—it is not itself a living machine, but a part of one. So, if the term "living molecule" is used to describe a virus, one runs the risk of having it accepted in a more complete sense than it should be.

In regard to the origin of life, some seem to have been led to the idea that if a virus particle were once formed, or even if a nucleic acid molecule

or long polynucleotide were formed, then life could be said to have originated. Clearly such an event would not in itself include the origin of the machinery for replication of the virus or nucleic acid template—rather, the existence of a virus would indicate that the machinery already existed. This machinery, which as we have seen contains a thermodynamic and kinetic component as well as a template, is essential for evolution to the present array of living species.

I am not sure where the term "naked gene" originated but I know that I at one time used it myself and that this may have led to a misinterpretation of what I wished to express (see, Blum (1962), Chap. XI with addendum). The modern concept of the gene seems to be that it is a template; probably a locus in a nucleic acid molecule (DNA). Under these circumstances a naked gene becomes rather difficult to define. I myself associated the term with naked template molecules—at the time I thought in the terms of protein rather than nucleic acid templates—which were floating in a medium that provided the necessary mechanism for replication of these templates. That such a non-cellular stage occurred at an early life stage can be legitimately imaged if one's imagination includes some machinery for replication.[10] But, if we loosely think of the gene as being self-replicating then we are up against the same difficulty as with the idea that viruses are living molecules; indeed the analogy is very close and much of recent thinking about the nature of the gene contains analogy to viruses.

I may point out that the adult sperm cell which of course contains many genes is, like the virus, incapable of self-replication. The sperm must be introduced into the egg before the genes which it contains can be replicated, just as the virus requires the host cell for its replication. So in this respect we would be justified in saying that the sperm is not a complete living cell but a part of a living machine that includes the egg cell. This is of course a matter of definition such as should not be permitted to lead us astray from the strict sense of the argument that the replication of genetic pattern essential for the perpetuation and evolution of living organisms requires a machine, of which the template that contains the pattern is only a part.

Some Implications

What are the implications of the argument that has just been presented? First, let us review the similarities and differences between

[10] It is, of course, possible that the first replicating machines developed in coacervate droplets, as suggested by Oparin (1957, and see Fox (1960)). But while such a separation into droplets may have in some way favored replication and laid the basis for the cellular character of living organisms, it does not in itself explain the origin of the cyclic machinery required for replication.

choice of mutants by natural selection and choice of reaction pathways in non-living systems. Perhaps the differences and the similarities one sees depend somewhat on where one stands. I think most biologists recognize intuitively a difference between the two processes, whereas chemists may stress the similarities. Applying the same framework of physicochemical mechanism, as I have attempted here, may emphasize similarities, tending to subordinate the differences in evolutionary result. But the functional differences remain nevertheless real.

In chemical evolution in a non-living world the direction of the pathway taken is a function of thermodynamics and kinetics, even when the expected direction of reaction is upset by radiant energy or other physical factors. In such a system, the reaction pathway may respond immediately and directly to a change in the environment, say the introduction of a catalyst which speeds up a given reaction step. The catalyst may be a product of the reaction itself, which then is an autocatalytic reaction; but this does not alter the picture very much because it is difficult to distinguish between such a reaction system and its environment. In the living, replicating system, on the other hand, this distinction is more clear-cut, there being little direct influence—and virtually no specific influence—of the external environment on replication of pattern. In chemical reaction, a given molecule which has reached a high enough energy level to react is for the moment different from its fellows to that extent; but, the reaction once achieved, that particular molecule is not distinguishable from other product molecules. The molecule does not maintain its individuality with respect to its energy content beyond a fraction of a second—the product state represents a new average condition, so in the long run it is the average and not the individual that counts. The same argument applies to formation of free radicals or intermediates in chemical reactions, which are transitory steps in the reaction that do not replicate and so perpetuate their kind.

Presumably, mutation too involves a temporary increase in energy at some place in the molecule in order to get over a barrier, but this is a fleeting change. In the case of a "successful" mutation the resultant alteration in pattern is maintained by replication. The individuality of the mutant pattern may thus be preserved for a very long time, being duplicated over and over again and so persisting through many generations, long after the particular molecule that was originally altered has ceased to exist as such. There is a sort of "memory" in this process that does not enter into strictly chemical evolution. Natural selection of a new pattern is a slow process in which many generations may be involved in accomplishing a single step; it amounts to picking out altered replicating patterns, that is, mutated genes. This is not accomplished directly, but by the overt changes the mutation produces in a larger system, the cell or multicellular organism, that contains the new pattern.

Thus the gene is isolated from direct impingement of the environment upon it; and if we wish to consider natural selection as a feed-back mechanism we must include the environment in our system, and the impingement of the organism and environment may be difficult to analyze (e.g., see Scholander, (1955); Blum (1961)).

We see from all this that living machines may, in a sense, arrest the ordinary time course of events to an extent not paralleled in any simple, cyclic, physical, or chemical system, at least any that I am able to picture. And this offers correspondingly greater opportunity for the development of complexity in the living world as compared to the nonliving.

Does the picture I have presented modify in any way our ideas about evolution by natural selection? Basically I think it strengthens the concept by giving it a more intimate and plausible physical basis. It is a great tribute to Charles Darwin that we are still seeking today in the light of a century of scientific progress to explain with greater exactitude the principle he laid down, and which we still accept. But, on the other hand, consideration of the more intimate mechanism may tend to weaken our anticipation of perfection in the results of evolution by natural selection. It emphasizes to us that while mutations may be regarded as accidental events there are great limitations as to the kinds of accidents that can occur. Fundamentally these limitations are set by properties of the molecules that make up the cell; but how much these properties have influenced the course of evolution by natural selection would be difficult to express in rigorous form. It is also difficult to know to just what extent one must attribute the direction taken by biological evolution to the direction taken by the chemical evolution that preceded it. We find reason to think that some substances are common to all living systems because they were present at the beginning as the result of previous chemical evolution. The amino acids, for example, seem already to be reasonably accounted for in this way, and no doubt other essential components of living material will be. There are certain dominant themes in the biochemical tapestry, but there are many details that seem to have been woven with considerable vagary suggesting both the guiding hand of natural selection and incidental "accidents" of mutation, some of which may have little or no survival value. We are constrained to view the role of natural selection in terms of the fossil record since the beginning of the Cambrian, 500 million years ago; and one of the things this record tells us, when we combine the evidence with that of comparative biochemistry, is that the major molecular patterns of inheritance must have been pretty well-established before that time. What has happened since would seem to have involved relatively small changes, considering the degree of biological organization already established then. But living systems had existed and evolution has been going on for a long time

before the beginning of the Cambrian—possibly for two or three thousand million years. The major themes of organic evolution were established in the course of this earlier period, and it seems likely that strictly physico-chemical factors played a more prominent role in setting limits upon the direction natural selection could take then than they did later.

But however the limits were set they must have continued to restrict the possible directions evolution might take. The first replicable and mutable cell would seem to have had before it the possibility of vastly more mutations than has any modern cell of any existent species. Of course, I do not mean by this that the primordial living system contained in a physical sense all these possible patterns, for surely more became possible by recombinations in the course of the many millions of years of evolution than were present in the first living machine. What I mean to say is that the limitations on the direction of evolution are much greater for any existing species than they were for the primordial system from which it ultimately stems. The limitations imposed by physico-chemical factors upon the possible directions of mutation must constitute restrictions on the degree of perfection of adaptation to environment. I think this is sometimes lost sight of. There seems to be widespread tendency to disregard such limitations and to assume complete randomness of mutation, which may encourage overemphasis of the perfection of adaptation of the organism to the environment, and encourage a kind of teleology that may be misleading—we may risk turning Darwinism into a cult. This may also encourage false social analogies.

As regards the idea of randomness in mutation, we must remember that this is something we use as a tool and should not let it confuse us in thinking about evolution in an over-all or global sense. What we mean by randomness of mutation is that at a given instant, given a particular set of conditions, there is an array of possibilities for mutation; and for purposes of analysis, we may proceed to treat this array as though it were a fixed thing. But thinking evolutionarily we see that the possibilities for mutation are continually changing, and the environment as well, and that used in this way the term, randomness, only applies to a given instant we have chosen to study.

The question whether life exists on other worlds and how it originated there has occupied thinkers for a long time but there has been recent increase in interest, particularly since Sputnik and the development of the so-called Space Age. With recognition of the vast extent of the universe, which seems only to grow larger as we extend our observations, there has been a tendency to people this universe with living organisms. It may be estimated that there is a very large number of planets in our galaxy that are sufficiently like our earth to support life as we know it.[11]

[11] The conditions may really be quite limiting (see, Henderson (1913); Blum (1962).

But to assume on this basis that such life exists there, tacitly admits that, given the same kind of a chemical environment as once existed on our earth, living organisms will come into being as a matter of course. If the conditions for origin of life are more exacting, the probabilities become less, however, and such estimates need to be revised downward. From what has just been said it seems that one should assume more specific conditions than just an appropriate mixture of molecular species in order for a living, replicating machine to arise. Just how detailed the specifications were to permit the origin of life on this planet, and just how many rarely probable events were involved, it would be very difficult to estimate. When we think of the broad array of living species which exists, we realize that their evolution by natural selection has also involved a great many rare events. For each mutation represents a rare event and there must have been many mutations involved in the evolution of each species. As we look back, it appears that had things happened in slightly different ways our present array of species might be quite different. The farther back we go the more critical the picture becomes, that is, a mutation happening sometime early in pre-Cambrian time might have had much more effect on the direction of evolution of species than a mutation that occurred, say only a few million years ago. If we include in our thinking Man's cultural evolution, which has entailed many rare events of a still different kind, we see that the chances of finding beings very much like ourselves elsewhere in the galaxy may be small indeed, even though there may be many planets that could have accommodated them, had the hazards of history followed the same course. That there may somewhere be replicating machines constituted from the same molecular species as our own seems somewhat more likely, but the conditions and sequence of events that were required to establish them may make this, too, a tenuous possibility. Such thinking should, perhaps, not dampen enthusiasm for the exploration of the possibility of life on other planets, but it might temper our expectations of what we may find, and affect planning as regards what to look for.

A great deal of what I have said in this paper has, of course, been in the nature of speculation, but I hope that I have paid reasonable respect to established observation and theory in the various fields of science it has been necessary to touch upon. No doubt I have stretched both the chemical and the biological picture but I hope I have not distorted them unduly in trying to get them into the same frame. It seems to me it is time to take that risk; for have we not been trying for too long to approach many problems of life from opposite ends, with only a vague hope that we may somehow come together in the middle.

REFERENCES

ABELSON, P. H. 1957. Some aspects of paleobiochemistry. *Annals N. Y. Acad. Sci., 69,* 255–376.

BERNAL, J. D. 1951. *The Physical Basis of Life,* Routledge and Kegan Paul, London. Also in *Proc. Physical Soc.,* (1949) *62,* 537.

BLUM, H. F. 1935. A consideration of evolution from a thermodynamic view-point. *Am. Naturalist, 69,* 354–369.

BLUM, H. F. 1957. On the origin of self-replicating systems. In *Rhythmic and Synthetic Growth Processes.* ed. D. Rudnick. Princeton Univ. Press.

BLUM, H. F. 1962. *Time's Arrow and Evolution.* Revised edition. Harper Bros., New York. (in course of publication). Earlier Editions (1951, 1955) Princeton Univ. Press.

BLUM, H. F. 1961. Does the melanin pigment of human skin have adaptive value? *Quart. Rev. Biol., 36,* 50–63.

BORSOOK, H., and DUBNOFF, J. W. 1940. The biological synthesis of hippuric acid in vitro. *J. Biol. Chem., 132,* 307–324.

FLORKIN, M. *L'Evolution Biochimique* (1944) Desoer, Liège. English translation, *Biochemical Evolution* (1949) Academic Press, New York.

FOX, S. W. How did life begin. *Science* (1960), *132,* 200–208.

HARDY, W. B. 1934. *To Remind, A Biological Essay.* (The Abraham Flexner Lecture 1931) Williams and Wilkins, Baltimore. And (1936) in collected Papers, Cambridge University Press.

HENDERSON, L. J. 1913. *The Fitness of the Environment,* MacMillan, New York.

LINDERSTROM-LANG, K. V. 1952. *Proteins and Enzymes.* Stanford University Press. Stanford, Calif.

MILLER, S. L. (1953). A production of amino acids under possible primitive conditions. *Science, 117,* 528–529.

MILLER, S. L., and UREY, H. C. 1959. Organic compound synthesis on the primitive earth. *Science, 130,* 245–251.

OPARIN, A. I. 1957. *The Origin of Life on Earth.* 2nd ed. Oliver and Boyd, Edinburgh.

Proceedings of the First International Congress on the Origin of Life on Earth, Moscow 1957. (1959) Pergamon Press, New York. Selected papers are published under the title, *Aspects of the Origin of Life* (1960) ed. M. Florkin, Pergamon Press, New York.

SCHOLANDER, P. F. 1955. Evolution of climatic adaptation in homeotherms. *Evolution, 9,* 15–26.

WALD, G. 1957. The origin of optical activity. *Ann. N. Y. Acad. Sci., 69,* 255–376.