Nishina Memorial Lecture

Origins of Life

Freeman J. Dyson

Institute for Advanced Study, Princeton
New Jersey, USA

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given at Tokyo and Kyoto, October 1984.

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I. Illustrious Predecessors [Fig. 1]

First I would like to express my thanks to the Nishina Memorial Foundation, and to Professor Kubo in particular, for inviting me to give this lecture and making it possible for me to visit Japan. Unfortunately I never met Professor Nishina, and I knew him only by reputation, as the discoverer of the Klein-Nishina formula in quantum electrodynamics. That formula had tremendous importance in the history of physics. It was the first quantitative prediction of quantum electrodynamics in the relativistic domain to be verified experimentally. It gave the physicists of the 1930's and 1940's confidence that relativistic field theories were not total nonsense. Relativistic field theories described at least one experimental fact correctly. This confidence was the essential foundation on which Professor Tomonaga in Japan and Schwinger and Feynman in America built the structure of quantum electrodynamics as it now exists. All physicists who have taken part in the building of quantum electrodynamics, and later in the building of quantum chromodynamics, not only in Japan but all over the world, owe a great debt of gratitude to Professor Nishina.

But I did not come here today to talk about physics. Like other elderly physicists, I stop-

Fig. 1

ILLUSTRIOUS PREDECESSORS

YOSHIO NISHINA
ERWIN SCHRÖDINGER
MANFRED EIGEN
LESLIE ORGEL
LYNN MARGULIS
MOTOO KIMURA

ped some time ago to compete with the young people who are inventing new models every day to explain the intricate hierarchy of hadrons and leptons. I admire what the young people are doing, but I prefer to work in a less fashionable area where the pace is slower. I turned my attention to biology and in particular to the problem of the origin of life. This is a problem of chemistry rather than of physics, but a physicist may hope to make a modest contribution to its solution by suggesting ideas which chemical experiments can test. It would be absurd to imagine that the problem of the origin of life can be solved by theoretical speculation alone. Theoretical physicists entering the field of biology must behave with proper humility; our role is not to answer questions but only to ask questions which biologists and chemists may be able to answer.

Here [Fig. 2] is a short list of references for people who are not expert in biology. The Schrödinger book is a wonderful introduction to biology for physicists. I will come back to it presently. The Miller-Orgel book is a good general survery of the state of knowledge about the origin of life, written ten years ago but still useful. The authors are both chemists, and they do particularly well in explaining the details of the chemistry out of which life is supposed to have arisen. The article by Eigen and his collaborators is twice as long as a standard Scientific American article. It contains a full account of the experiments which Eigen and his group have done during the ten years since the Miller-Orgel book was written. These experiments started the "New Wave" in our thinking about the origin of life. The last reference is my own modest contribution to the subject. It contains a mathematically precise account of a model which I shall describe in a less formal fashion in this lecture.

"What is Life?" is a little book, less than a hundred pages long, published by the physicist Erwin Schrödinger forty years ago, when he was about as old as I am now. It was extraordinarily influential in guiding the thoughts of the young people who created the new science of molecular biology in the following decade. The book is clearly and simply written, with less than ten equations from beginning to end. It is also a fine piece of literature. Although Schrödinger was exiled from his native Austria to Ireland after the age of fifty, he wrote English far more beautifully than most of his English and American colleagues. He

Fig. 2

REFERENCES

S. L. Miller and L. E. Orgel: "The Origins of Life on the Earth" (Prentice-Hall, 1974)

M. Eigen, W. Gardiner, P. Schuster and R. Wikler-Oswatitsch: "The Origin of Genetic Information," *Scientific American*, 244, 88—118 (April, 1981)

F. Dyson: "A Model for the Origin of Life," *J. Molecular Evolution*, **18**, 344—350 (1982)

E. Schrödinger: "What is Life? The Physical Aspect of the Living Cell," (Cambridge University Press, 1944)

also knew how to ask the right questions. The basic questions which he asked in his book are the following: What is the physical structure of the molecules which are duplicated when chromosomes divide? How is the process of duplication to be understood? How do these molecules succeed in controlling the metabolism of cells? How do they create the organization that is visible in the structure and function of higher organisms? He did not answer these questions. But by asking them he set biology moving along the path which led to the epoch-making discoveries of the last forty years, to the double helix, the triplet code, the precise analysis and wholesale synthesis of genes, the quantitative measurement of evolutionary divergence of species.

Schrödinger showed wisdom not only in the questions which he asked but also in the questions he did not ask. He did not ask any questions about the origin of life. He understood that the time was ripe in 1944 for a fundamental understanding of the physical basis of life. He also understood that the time was not ripe for any fundamental understanding of life's origin. Until the basic chemistry of living processes was clarified, one could not ask meaningful questions about the possibility of spontaneous generation of these processes in a pre-biotic environment. He wisely left the question of origins to a later generation.

Now, forty years later, the time is ripe to ask the questions which Schrödinger avoided. The questions of origin are now becoming experimentally accessible, just as the questions of structure were becoming experimentally accessible in the nineteen-forties. Manfred Eigen is the chief explorer of the new territory. He is, after all, a chemist, and this is a job for chemists. Eigen and his colleagues in Germany have done experiments which show us biological organization originating spontaneously and evolving in a test-tube [Fig. 3]. More precisely, they have demonstrated that a solution of nucleotide monomers will under suitable conditions give rise to a nucleic acid polymer molecule which replicates and mutates and competes with its progeny for survival. From a certain point of view, one might claim that these experiments already achieved the spontaneous generation of life from non-life. They bring us at least to the point where we can ask and answer questions about the ability of nucleic acids to synthesize and organize themselves. Unfortunately, the conditions in Eigen's test-tubes are not really pre-biotic. To make his experiments work, Eigen put into the test-tubes a polymerase enzyme, a protein catalyst extracted from a living bacteriophage. The synthesis and replication of the nucleic acid is dependent on the structural guidance provided by the enzyme. We are still far from an experimental demonstration of the appearance of biological order without the help of a biologically-derived precursor. Nevertheless, Eigen has provided the tools with which we may begin to attack the problem of origins. He has brought the origin of life out of the domain of idle speculation and into the domain of experiment.

I should also mention at this point three other pioneers who have done the most to clarify

Fig. 3   BIEBRICHER-EIGEN-LUCE Experiment.
                                   Replication of RNA in a test-tube. (1981)
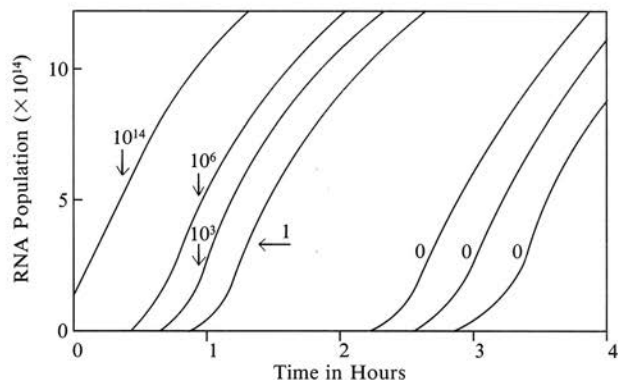
In the test-tube:
  Ample supply of nucleotide monomers 10^{14} molecules of Q_β replicase enzyme
  Number of RNA template molecules marked for each curve

my thinking about the origin of life. One is the chemist Leslie Orgel who originally kindled my interest in this subject twenty years ago, one is the biologist Lynn Margulis, and one is the geneticist Motoo Kimura here in Japan. Leslie Orgel is, like Manfred Eigen, an experimental chemist. He taught me most of what I know about the chemical antecedents of life. He has done experiments complementary to those of Eigen. Eigen was able to make RNA grow out of nucleotide monomers without having any RNA template for the monomers to copy, but with a polymerase enzyme to tell the monomers what to do. Orgel has done equally important experiments in the opposite direction. Orgel demonstrated that nucleotide monomers will under certain conditions make RNA if they are given an RNA template to copy, without any polymerase enzyme. Orgel found that zinc ions in the solution are a good catalyst for the RNA synthesis. It may not be entirely coincidental that many modern biological enzymes have zinc ions in their active sites. To summarize, Eigen made RNA using an enzyme but no template, and Orgel made RNA using a template but no enzyme. In living cells we make RNA using both templates and enzymes. If we suppose that RNA was the original living molecule, then to understand the origin of life we have to make RNA using neither a template nor an enzyme [Fig. 4]. Neither Eigen nor Orgel has come close to achieving this goal. Their experiments have given us two solid foundations of knowledge, with a wide river of ignorance running between them. Since we have solid ground on the two sides, it is not hopeless to think of building a bridge over the river. A bridge in science is a theory.

Fig. 4

RNA EXPERIMENTS

1. Biebricher, Eigen and Luce (1981)
    Nucleotides ⎤
    Replicase Enzyme ⎬ →RNA
    No template ⎦

2. Lohrmann, Bridson and Orgel (1980)
    Nucleotides ⎤
    Template RNA ⎬
    Zinc (or Magnesium) ⎬ →RNA
    No enzyme ⎦

3. Biological Replication *in vivo*
    Nucleotides ⎤
    Template RNA ⎬ →RNA
    Replicase enzyme ⎦

4. Hypothetical Pre-biotic Synthesis
    Nucleotides ⎤
    No template ⎬ →RNA
    No enzyme ⎦

When bridges are to be built, theoretical scientists may have a useful role to play.

Lynn Margulis is one of the chief bridge-builders in modern biology. She built a bridge between the facts of cellular anatomy and the facts of molecular genetics. Her bridge was the idea that parasitism and symbiosis were the driving forces in the evolution of cellular complexity. She did not invent this idea, but she was its most active promoter and systematizer. She collected the evidence to support her view that the main internal structures of eucaryotic cells did not originate within the cells but are descended from independent living creatures which invaded the cells from outside like carriers of an infectious disease. The invading creatures and their hosts then gradually evolved into a relationship of mutual dependence, so that the erstwhile disease organism became by degrees a chronic parasite, a symbiotic partner, and finally an indispensable part of the substance of the host. This Margulis picture of early cellular evolution now has incontrovertible experimental support. The molecular structures of chloroplasts and mitochondria are found to be related more closely to alien bacteria than to the cells in which they have been incorporated for one or two billion years. But there are also general philosophical reasons for believing that the Margulis picture will be valid even in cases where it cannot be experimentally demonstrated. A living

cell, in order to survive, must be intensely conservative. It must have a finely tuned molecular organization and it must have efficient mechanisms for destroying promptly any molecules which depart from the overall plan. Any new structure arising within this environment must be an insult to the integrity of the cell. Almost by definition, a new structure will be a disease which the cell will do its best to resist. It is possible to imagine new structures arising internally within the cell and escaping its control, like a cancer growing in a higher organism. But it is much easier to imagine new structures coming in from the outside like infectious bacteria, already prepared by the rigors of independent living to defend themselves against the cell's efforts to destroy them.

The last on my list of illustrious predecessors is the geneticist Motoo Kimura. Kimura developed the mathematical basis for a statistical theory of molecular evolution, and he has been the chief advocate of the neutral theory of evolution. The neutral theory says that, through the history of life from beginning to end, random statistical fluctuations have been more important than Darwinian selection in causing species to evolve. Evolution by random statistical fluctuation is called genetic drift. Kimura maintains that genetic drift drives evolution more powerfully than natural selection. I am indebted to Kimura in two separate ways. First, I use Kimura's mathematics as a tool for calculating the behavior of molecular populations. The mathematics is correct and useful, whether you believe in the neutral theory of evolution or not. Second, I find the neutral theory helpful even though I do not accept it as dogma. In my opinion, Kimura has overstated his case, but still his picture of evolution may sometimes be right. Genetic drift and natural selection are both important, and there are times and places where one or the other may be dominant. In particular, I find it reasonable to suppose that genetic drift was dominant in the very earliest phase of biological evolution, before the mechanisms of heredity had become exact. Even if the neutral theory is not true in general, it may be a useful approximation to make in building models of pre-biotic evolution.
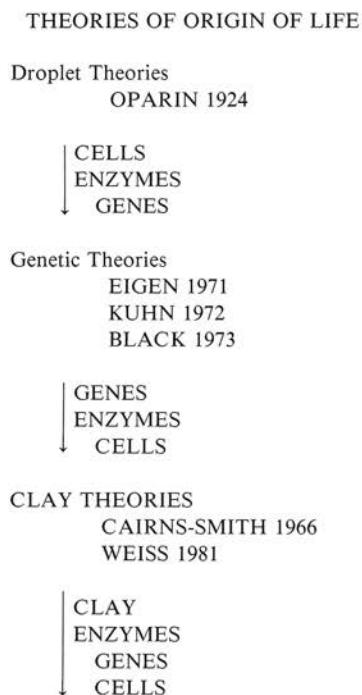
We know almost nothing about the origin of life. We do not even know whether the origin was gradual or sudden. It might have been a process of slow growth stretched out over millions of years, or it might have been a single molecular event that happened in a fraction of a second. As a rule, natural selection is more important over long periods of time and genetic drift is more important over short periods. If you think of the origin of life as slow, you must think of it as a Darwinian process driven by natural selection. If you think of it as quick, the Kimura picture of evolution by statistical fluctuation without selection is appropriate. In reality the origin of life must have been a complicated process, with incidents of rapid change separated by long periods of slow adaptation. A complete description needs to take into account both drift and selection. In my calculations I have made use of the theorist's privilege to simplify and idealize a natural process. I have considered the origin of

life as an isolated event occurring on a rapid time-scale. In this hypothetical context, it is consistent to examine the consequences of genetic drift acting alone. Darwinian selection will begin its work after the process of genetic drift has given it something to work on.

II. Theories of the Origin of Life

There are three main groups of theories about the origin of life. I call them after the names of their most famous advocates, Oparin, Eigen and Cairns-Smith. I have not done the historical research that would be needed to find out who thought of them first [Fig. 5]. The Oparin theory was described in Oparin's book "Proiskhozhdenie Zhizni" in 1924, long before anything was known about the structure and chemical nature of genes. Oparin supposed that the order of events in the origin of life was: cells first, enzymes second, genes third. He observed that when a suitably oily liquid is mixed with water it sometimes happens

Fig. 5

THEORIES OF ORIGIN OF LIFE

Droplet Theories
    OPARIN 1924

        CELLS
        ENZYMES
         GENES

Genetic Theories
    EIGEN 1971
    KUHN 1972
    BLACK 1973

        GENES
        ENZYMES
         CELLS

CLAY THEORIES
    CAIRNS-SMITH 1966
    WEISS 1981

        CLAY
        ENZYMES
         GENES
         CELLS

that the two liquids form a stable mixture called a coacervate, with the oily liquid dispersed into small droplets which remain suspended in the water. Coacervate droplets are easily formed by non-biological processes, and they have a certain superficial resemblance to living cells. Oparin proposed that life began by the successive accumulation of more and more complicated molecular populations within the droplets of a coacervate. The physical framework of the cell came first, provided by the naturally occurring droplet. The enzymes came second, organizing the random population of molecules within the droplet into self-sustaining metabolic cycles. The genes came third, since Oparin had only a vague idea of their function and they appeared to him to belong to a higher level of biological organization than enzymes.

The Oparin picture was generally accepted by biologists for half a century. It was popular, not because there was any evidence to support it, but rather because it seemed to be the only alternative to biblical creationism. Then, during the last twenty years, Manfred Eigen provided another alternative by turning the Oparin theory upside-down. The Eigen theory reverses the order of events. It has genes first, enzymes second and cells third. It is now the most fashionable and generally accepted theory. It has become popular for two reasons. First, the experiments of Eigen and of Orgel use RNA as working material and make it plausible that the replication of RNA was the fundamental process around which the rest of biology developed. Second, the discovery of the double helix showed that genes are structurally simpler than enzymes. Once the mystery of the genetic code was understood, it became natural to think of the nucleic acids as primary and of the proteins as secondary structures. Eigen's theory has self-replicating RNA at the beginning, enzymes appearing soon afterwards to build with the RNA a primitive form of the modern genetic transcription apparatus, and cells appearing later to give the apparatus physical cohesion.

The third theory of the origin of life, the theory of Cairns-Smith, is based upon the idea that naturally occurring microscopic crystals of the minerals contained in common clay might have served as the original genetic material before nucleic acids were invented. The microcrystals of clay consist of a regular silicate lattice with a regular array of ionic sites, but with an irregular distribution of metals such as magnesium and aluminum occupying the ionic sites. The metal ions can be considered as carriers of information like the nucleotide bases in a molecule of RNA. A microcrystal of clay is usually a flat plate with two plane surfaces exposed to the surrounding medium. Suppose that a microcrystal is contained in a droplet of water with a variety of organic molecules dissolved in the water. The metal ions embedded in the plane surfaces form irregular patterns of electrostatic potential which can adsorb particular molecules to the surfaces and catalyze chemical reactions on the surfaces in ways dependent on the precise arrangement of the ions. In this fashion the information contained in the pattern of ions might be transferred to chemical species dissolved in the

water. The crystal might thus perform the same function as RNA in guiding the metabolism of amino-acids and proteins. Moreover, it is conceivable that the clay microcrystal can also replicate the information contained in its ions. When the crystal grows by accreting silicate and metal ions from the surrounding water, the newly accreted layer will tend to carry the same pattern of ionic charges as the layer below it. If the crystal is later cut along the plane separating the old from the new material, we will have a new exposed surface replicating the original pattern. The clay crystal is thus capable in principle of performing both of the essential functions of a genetic material. It can replicate the information which it carries, and it can transfer the information to other molecules. It can do these things in principle. That is to say, it can do them with some undetermined efficiency which may be very low. There is no experimental evidence to support the statement that clay can act either as a catalyst or as a replicator with enough specificity to serve as a basis for life. Cairns-Smith asserts that the chemical specificity of clay is adequate for these purposes. The experiments to prove him right or wrong have not been done.

The Cairns-Smith theory of the origin of life has clay first, enzymes second, cells third and genes fourth. The beginning of life was a natural clay crystal directing the synthesis of enzyme molecules adsorbed to its surface. Later, the clay and the enzymes learned to make cell membranes and became encapsulated in cells. The original living creatures were cells with clay crystals performing in a crude fashion the functions performed in a modern cell by nucleic acids. This primaeval clay-based life may have existed and evolved for many millions of years. Then one day a cell made the discovery that RNA is a better genetic material than clay. As soon as RNA was invented, the cells using RNA had an enormous advantage in metabolic precision over the cells using clay. The clay-based life was eaten or squeezed out of existence and only the RNA-based life survived.

At the present time there is no compelling reason to accept or to reject any of the three theories. Any of them, or none of them, could turn out to be right. We do not yet know how to design experiments which might decide between them. I happen to prefer the Oparin theory, not because I think it is necessarily right but because it is unfashionable. In recent years the attention of the experts has been concentrated upon the Eigen throry, and the Oparin theory has been neglected. The Oparin theory deserves a more careful analysis in the light of modern knowledge. For the rest of this lecture I shall be talking mostly about my own attempt to put the Oparin theory into a modern framework using the mathematical methods of Kimura.

Another reason why I find the Oparin theory attractive is that it fits well into the general picture of evolution portrayed by Lynn Margulis. According to Margulis, most of the big steps in cellular evolution were caused by parasites. I would like to propose the hypothesis that nucleic acids were the oldest and most successful cellular parasites. I am extending the

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scope of the Margulis picture of evolution to include not only eucaryotic cells but pro-caryotic cells as well. I propose that the original living creatures were cells with a metabolic apparatus directed by protein enzymes but with no genetic apparatus. Such cells would lack the capacity for exact replication but could grow and divide and reproduce themselves in an approximate statistical fashion. They might have continued to exist for millions of years, gradually diversifying and refining their metabolic pathways. Amongst other things, they discovered how to synthesize ATP, adenosine triphosphate, the magic molecule which serves as the principal energy-carrying intermediate in all modern cells. Cells carrying ATP were

Fig. 6

ATP and AMP
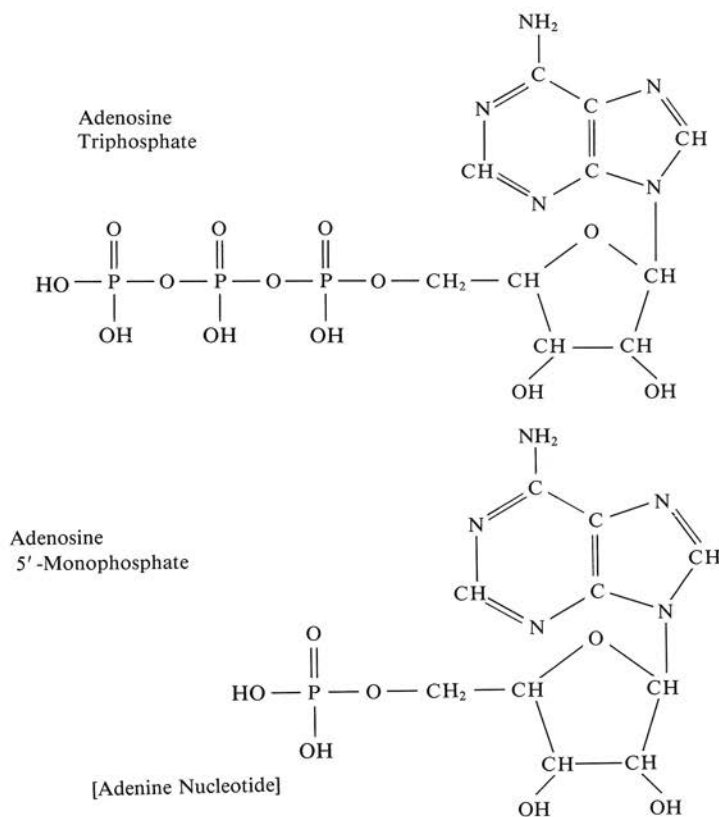
able to function more efficiently and prevailed in the Darwinian struggle for existence. In time it happened that cells were full of ATP and other related molecules such as AMP, adenosine monophosphate, GMP, guanine monophosphate, and so on.

Now we observe the strange fact that the two molecules ATP and AMP, having almost identical chemical structures, have totally different but equally essential functions in modern cells [Fig. 6]. ATP is the universal energy-carrier. AMP is one of the nucleotides which make up RNA and function as bits of information in the genetic apparatus. GMP is another of the nucleotides in RNA. To get from ATP to AMP, all you have to do is replace a triple phosphate group by a single phosphate radical. I am proposing that the primitive cells had no genetic apparatus but were saturated with molecules like AMP and GMP as a result of the energy-carrying function of ATP. This was a dangerously explosive situation. In one cell which happened to be carrying an unusually rich supply of nucleotides, an accident occurred. The nucleotides began doing the Eigen experiment on RNA synthesis three billion years before it was done by Eigen. Within the cell, with some help from pre-existing enzymes, the nucleotides produced an RNA molecule which then continued to replicate itself. In this way RNA first appeared as a parasitic disease within the cell. The first cells in which the RNA disease occurred probably became sick and died. But then, according to the Margulis scheme, some of the infected cells learned how to survive the infection. The protein-based life learned to tolerate the RNA-based life. The parasite became a symbiont. And then, very slowly over millions of years, the protein-based life learned to make use of the capacity for exact replication which the chemical structure of RNA provided. The primal symbiosis of protein-based life and parasitic RNA grew gradually into a harmonious unity, the modern genetic apparatus.

This view of RNA as the oldest and most incurable of our parasitic diseases is only a

Fig. 7

ARGUMENTS SUPPORTING ORIGIN
OF RNA AS CELLULAR PARASITE

1.   This is extension of Margulis view, proved correct for eucaryotic cells, back into the pro-caryotic era.

2.   Hardware (protein) should come before Software (nucleic acids).

3.   Amino-acid synthesis is easier than nucleotide synthesis.

4.   Nucleotides might have been by-product of ATP metabolism.

5.   The hypothesis may be testable.

poetic fancy, not yet a serious scientific theory. Still it is attractive to me for several reasons [Fig. 7]. First, it is in accordance with our human experience that hardware should come before software. The modern cell is like a computer-controlled chemical factory in which the proteins are the hardware and the nucleic acids are the software. In the evolution of machines and computers, we always developed the hardware first before we began to think about software. I find it reasonable that natural evolution should have followed the same pattern. A second argument in favor of the parasite theory of RNA comes from the chemistry of amino-acids and nucleotides. It is easy to synthesize amino-acids, the constituent parts of proteins, out of plausible pre-biotic materials such as water, methane and ammonia. The synthesis of amino-acids from a hypothetical reducing atmosphere was demonstrated in the classic experiment of Miller in 1953. The nucleotides which make up nucleic acids are much more difficult to synthesize. Nucleotide bases such as adenine and guanine have been synthesized by Oró from ammonia and hydrocyanic acid. But to go from a base to a complete nucleotide is a more delicate matter. Furthermore, nucleotides once formed are less stable than amino-acids. Because of the details of the chemistry, it is much easier to imagine a pond on the pre-biotic earth becoming a rich soup of amino-acids than to imagine a pond becoming a rich soup of nucleotides. Nucleotides would have had a better chance to polymerize if they originated in biological processes inside already existing cells. My third reason for liking the parasite theory of RNA is that it may be experimentally testable. If the theory is true, living cells may have existed for a very long time before becoming infected with nucleic acids. There exist microfossils, traces of primitive cells, in rocks which are more than 3 billion years old. It is possible that some of these microfossils might come from cells older than the origin of RNA. It is possible that the microfossils may still carry evidence of the chemical nature of the ancient cells. For example, if the microfossils were found to preserve in their mineral constituents significant quantities of phosphorus, this would be strong evidence that the ancient cells already possessed something resembling a modern genetic apparatus. So far as I know, no such evidence has been found. I do not know whether the processes of fossilization would be likely to leave chemical traces of nucleic acids intact. So long as this possibility exists, we have the opportunity to test the hypothesis of a late origin of RNA by direct observation.

III. The Error Catastrophe

The central difficulty confronting any theory of the origin of life is the fact that the modern genetic apparatus has to function almost perfectly if it is to function at all. If it does not function perfectly, it will give rise to errors in replicating itself, and the errors will accumulate from generation to generation. The accumulation of errors will result in a pro-

gressive deterioration of the system until it is totally disorganized. This deterioration of the replication apparatus is called the "error catastrophe."

Manfred Eigen has given us a simple mathematical statement of the error catastrophe as follows [Fig. 8]. Suppose that a self-replicating system is specified by N bits of information, and that each time a single bit is copied from parent to daughter the probability of error is ε. Suppose that natural selection operates to penalize errors by a selection factor S. That is to say, a system with no errors has a selective advantage S over a system with one error, and so on. Then Eigen finds the criterion for survival to be

$$N\varepsilon < \log S \qquad (3.1)$$

If the condition (3.1) is satisfied, the selective advantage of the error-free system is great enough to maintain a population with few errors. If the condition (3.1) is not satisfied, the error catastrophe occurs and the replication cannot be sustained. The meaning of (3.1) is easy to interpret in terms of information theory. The left side $N\varepsilon$ of the inequality is the number of bits of information lost by copying errors in each generation. The right side ($\log S$) is the number of bits of information supplied by the selective action of the environment. If the information supplied is less than the information lost in each generation, a progressive degeneration is inevitable.

The condition (3.1) is very stringent. Since the selective advantage of an error-free system cannot be astronomically large, the logarithm cannot be much greater than unity. To satisfy (3.1) we must have an error-rate of the order of N^{-1} at most. This condition is barely satisfied in modern higher organisms which have N of the order of 10^8 and ε of the order of 10^{-8}. To achieve an error-rate as low as 10^{-8} the modern organisms have evolved an extremely elaborate system of double-checking and error-correcting within the replication system. Before any of this delicate apparatus existed, the error-rates must have been much higher. The condition (3.1) thus imposes severe requirements on any theory of the origin of life which, like Eigen's theory, makes the replication of RNA a central element of life from the beginning.

Fig. 8   THE ERROR CATASTROPHE

In Eigen quasi-species model of RNA replication.

Good molecules can survive the multiplication of errors only if Log (Selective advantage) $\geq$ (Error rate) $\times$ (Gene length).

Error rate must be $\leq 10^{-2}$ if genes carry useful amount of information.

In Eigen-Biebricher experiment average RNA length was 120 nucleotides. This is consistent with error-rate 10^{-2} in presence of Q_β replicase enzyme.

Question: Is error-rate 10^{-2} possible in pre-biotic soup without enzymes?

All the experiments which have been done with RNA replication under abiotic conditions give error-rates of the order of 10^{-2} at best. If we try to satisfy (3.1) without the help of pre-existing organisms, we are limited to a replication-system which can describe itself with less than 100 bits of information. 100 bits of information is far too few to describe any interesting protein chemistry. This does not mean that Eigen's theory is untenable. It means that Eigen's theory requires an information-processing system which is at the same time extraordinarily simple and extraordinarily free from error. We do not know how to achieve such low error-rates in the initial phases of life's evolution.

I chose to study the Oparin theory because it offers a possible way of escape from the error catastrophe. In the Oparin theory the origin of life is separated from the origin of replication. The first living cells had no system of precise replication and could therefore tolerate high error-rates. The main advantage of the Oparin theory is that it allows early evolution to proceed in spite of high error-rates. It has the first living creatures consisting of populations of molecules with a loose organization and no genetic fine-tuning. There is a high tolerance for errors because the metabolism of the population depends only on the catalytic activity of a majority of the molecules. The system can still function with a substantial minority of in-effective or uncooperative molecules. There is no requirement for unanimity. Since the statistical fluctuations in the molecular polulations will be large, there is a maximum opportunity for genetic drift to act as driving force of evolution.

IV. A Toy Model of the Oparin Theory

I now stop talking about general principles. Instead I will describe a particular mathematical model which I call a Toy Model of the Oparin Theory. The word Toy means that the model is not intended to be realistic. It leaves out all the complicated details of real organic chemistry. It represents the processes of chemical catalysis by a simple abstract mathematical formula. Its purpose is to provide an idealized picture of molecular evolution which resembles in some qualitative fashion the Oparin picture of the origin of life. After I have described the toy model and deduced its consequences, I will return to the question whether the behavior of the model has any relevance to the evolution of life in the real world. The model is an empty mathematical frame into which we may later try to fit more realistic descriptions of pre-biotic evolution. My analysis of the model is only an elementary exercise in population biology, using equations borrowed from Fisher and Kimura. The equations are the same, whether we are talking about a population of molecules in a droplet or about a population of birds on an island.

To define the model, I make a list of ten assumptions [Fig. 9]. The list begins with general statements, but by the time we get to the end the model will be uniquely defined. This makes

Fig. 9

ASSUMPTIONS OF THE TOY MODEL

1. Cells came first, enzymes second, genes much later (Oparin).

2. A cell is an inert droplet containing a population of monomer units combined into polymer chains.

3. No death of cells. No Darwinian selection. Evolution by genetic drift.

4. Population changes by single substitution mutations.

5. Each of N monomers mutates with equal probability $(1/N)$.

6. Monomers are either active (correct) or inactive (incorrect).

7. Active monomers are in sites where they catalyze correct placement of other monomers.

it easy to generalize the model by modifying only the more specific assumptions.

Assumption 1 (Oparin Theory). Cells came first, enzymes second, genes much later.

Assumption 2. A cell is an inert droplet containing a population of polymer molecules which are confined to the cell. The polymers are composed of monomer units which we may imagine to be similar to the amino-acids which make modern proteins. The polymers in the cell contain a fixed number N of monomers. In addition there is an external supply of free monomers which can diffuse in and out of the cell, and there is an external supply of energy which causes chemical reactions between polymers and monomers.

Assumption 3. Cells do not die and do not interact with one another. There is no Darwinian selection. Evolution of the population of molecules within a cell proceeds by random drift.

Assumption 4. Changes of population occur by discrete steps, each step consisting of a single substitution mutation. A mutation is a replacement of one monomer by another at one of the sites in a polymer. This assumption is unnecessarily restrictive and is imposed only for the sake of simplicity. At the cost of some complication of the mathematics, we could include a more realistic variety of chemical processes such as splitting and splicing of polymer chains or addition and subtraction of monomers.

Assumption 5. At every step, each of the N sites in the polymer population mutates with equal probability $(1/N)$. This assumption is also unrealistic and is made to keep the calculation simple.

Assumption 6. In a given population of polymers, the bound monomers can be divided in-

to two classes, active and inactive. This assumption appears to be uncontroversial, but it actually contains the essential simplification which makes the model mathematically tractable. It means that we are replacing the enormous multidimensional space of molecular configurations by a single Boolean variable taking only two values, one for "active" and zero for "inactive."

Assumption 7. The active monomers are in active sites where they contribute to the ability of a polymer to act as an enzyme. To act as an enzyme means to catalyze the mutation of other polymers in a selective manner, so that correct species of monomer is chosen preferentially to move into an active site.

Assumption 8 [Fig. 10]. In a cell with a fraction x of monomers active, the probability that the monomer inserted by a fresh mutation will be active is $\varphi(x)$. The function $\varphi(x)$ represents the efficiency of the existing population of catalysts in promoting the formation of a new catalyst. The assumption that $\varphi(x)$ depends on x means that the activity of catalysts is to some extent inherited from the parent population to the newly mutated daughter. The form of $\varphi(x)$ expresses the law of inheritance from parent to daughter. The numerical value of $\varphi(x)$ will be determined by the details of the chemistry of the catalysts.

Assumption 8 is a drastic approximation. It replaces the average of the efficiencies of a population of catalysts by the efficiency of an average catalyst. I call it the "mean field approximation" since it is analogous to the approximation made in the Curie-Weiss mean-field model of a ferromagnet. In physics, we know that the mean-field approximation gives a good qualitative account of the behavior of a ferromagnet. In population biology, similar approximations have been made by Kimura. The effect of the mean-field approximation is to reduce the multidimensional random walk of molecular populations to a one-dimensional random walk of the single parameter x. Both in physics and in population biology, the

Fig. 10

ASSUMPTION 8

Mean-field approximation.
In a cell with a fraction x of units active, the probability of a mutated unit being active is $\varphi(x)$.
This reduces the multi-dimensional random walk of the molecular populations to the one-dimensional random walk of the single parameter x.
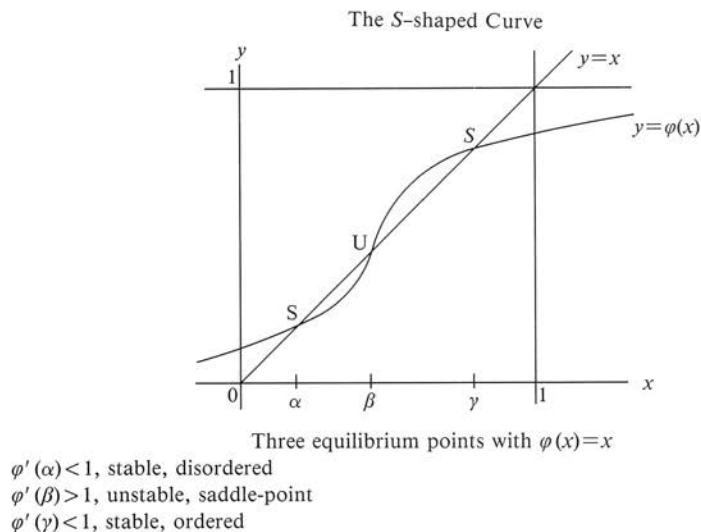
ASSUMPTION 9

Triple-crossing assumption.
The curve $y = \varphi(x)$ is S–shaped, crossing the line $y = x$ at three points $x = \alpha$, $x = \beta$, $x = \gamma$, between 0 and 1.

mean-field approximation may be described as pessimistic. It underestimates the effectiveness of local groupings of molecules in forming an ordered state. The mean-field approximation generally predicts a lower degree of order than is found in an exact theory.

Assumption 9 [Fig. 11]. The curve $y=\varphi(x)$ is S-shaped, crossing the line $y=x$ at three points $x=\alpha$, β, γ between zero and one. This assumption is again borrowed from the Curie-Weiss model of a ferromagnet. It means that the population of molecules has three possible equilibrium states. An equilibrium state occurs whenever $\varphi(x)=x$, since the law of inheritance then gives a daughter population with the same average activity x as the parent population. The equilibrium is stable if the slope of the curve $y=\varphi(x)$ is less than unity, unstable if the slope is greater than unity. Consider for example the lowest equilibrium state $x=\alpha$. I call it the disordered state because it has the smallest average activity. Since $\varphi'(\alpha)<1$, the equilibrium is stable. If a parent population has average activity x a little above α, the daughter population will tend to slide back down toward α. If the parent population has x a little below α the daughter population will tend to slide up toward α. The same thing happens at the upper equilibrium state $x=\gamma$. The upper state is also stable since $\varphi'(\gamma)<1$. I call it the ordered state because it has the largest catalytic activity. A population with activity x close to γ will move closer to γ as it evolves. But the middle equilibrium point $x=\beta$ is unstable since $\varphi'(\beta)>1$. If a population has x slightly larger than β, it will evolve

Fig. 11

The S-shaped Curve

Three equilibrium points with $\varphi(x)=x$

$\varphi'(\alpha)<1$, stable, disordered

$\varphi'(\beta)>1$, unstable, saddle-point

$\varphi'(\gamma)<1$, stable, ordered

away from β toward the ordered state $x=\gamma$, and if it has x slightly smaller that β it will slide away from β down to the disordered state $x=\alpha$. The equilibrium at $x=\beta$ is an unstable saddle-point.

We have here a situation analogous to the distinction between life and death in biological systems. I call the ordered state of a cell "alive," since it has most of the molecules working together in a collaborative fashion to maintain the catalytic cycles which keep them active. I call the disordered state "dead" since it has the molecules uncoordinated and mostly inactive. A population, either in the dead or in the alive state, will generally stay there for a long time , making only small random fluctuations around the stable equilibrium. However, the population of molecules in a cell is finite, and there is always the possibility of a large statistical fluctuation which takes the whole population together over the saddle-point from one stable equilibrium to the other. When a "live" cell makes the big statistical jump over the saddle-point to the lower state, we call the jump "death." When a "dead" cell makes the jump up over the saddle-point to the upper state, we call the jump "origin of life." When once the function $\varphi(x)$ and the size N of the population in the cell are given, the probabilities of "death" and of the "origin of life" can easily be calculated. We have only to solve a linear difference equation with the appropriate boundary conditions to represent an ensemble of populations of molecules diffusing over the saddle-point from one side or the other.

Assumption 10 [Fig.12]. Here we make a definite choice for the function $\varphi(x)$, basing the choice on a simple thermodynamic argument. It will turn out happily that the function $\varphi(x)$ derived from thermodynamics has the desired S-shaped form to produce the three equilibrium states required by Assumption 9.

We assume that every catalyst in the cell works by producing a difference between the activa-

Fig. 12

ASSUMPTION 10

Thermodynamics.

Assume every perfect catalyst lowers activation-energy for correct placement of a newly-placed unit by U.

In a population with fraction x of units active, each catalyst is assumed to lower activation-energy by xU.

This implies

$$\varphi(x)=\left(\frac{1}{1+ab^{-x}}\right),$$

$(1+a)$ is the number of species of monomer. $b=\exp(U/kT)$ is the discrimination factor of catalysts.

tion energies required for placing an active or inactive monomer into a mutating molecule. If the catalyst molecule is perfect, with all its monomer units active, then the difference in activation energies will be a certain quantity U which we assume to be the same for all perfect catalysts. If a catalyst is imperfect, in a cell with a fraction x of all monomer units active, we assume that it produces a difference xU in the activation energies for correct and incorrect mutations. We are here again making a mean-field approximation, assuming that the average effect of a collection of catalysts with various degrees of imperfection is equal to the effect of a single catalyst with its discrimination reduced by the average activity x of the whole population. This is another approximation which could be avoided in a more exact calculation.

We assume that the monomers belong to $(1+a)$ equally abundant species. This means that there is one right choice and a wrong choices for the monomer to be inserted in each mutation. The effect of the catalysts is to reduce the activation energy for the right choice by xU below the activation energy for a wrong choice. Thus the probability of a right choice is increased over the probability of each wrong choice by the factor

$$b^x \tag{4.1}$$

where

$$b = \exp [U/kT] \tag{4.2}$$

is the discrimination factor of a perfect catalyst at absolute temperature T, and k is Boltzmann's constant. We have a wrong choices with statistical weight unity compared to one right choice with statistical weight b^x. The function $\varphi(x)$ is the probability of a right choice at each mutation, and therefore

$$\varphi(x) = [1 + ab^{-x}]^{-1} \tag{4.3}$$

the same S-shaped function which appears in the mean-field model of a simple ferromagnet.

The formula (4.3) for $\varphi(x)$ completes the definition of the model. It is uniquely defined once the three parameters N, a, b are chosen. The three parameters summarize in a simple fashion the chemical raw material with which the model is working. N defines the size of the molecular population, a defines the chemical diversity of the monomer units, and b is the quality-factor defining the degree of discrimination of the catalysts.

We have now a definite three-parameter model to work with. It remains to calculate its consequences, and to examine whether it shows interesting behavior for any values of N, a, b which are consistent with the facts of organic chemistry. "Interesting behavior" here means the occurrence with reasonable probability of a jump from the disordered to the ordered state. We shall find that interesting behavior occurs for values of a and b lying in a narrow

range. This narrow range is determined only by the mathematical properties of the exponential function, and is independent of all physical or chemical constants. The model therefore makes a definite statement about the stuff out of which the first living cells were made. If the model has anything to do with reality, then the primaeval cells were composed of molecules having values of a and b within the calculated range.

It turns out that the preferred ranges of values of the three parameters are [Fig. 13]:

$$a \text{ from } 8 \text{ to } 10, \tag{4.4}$$

$$b \text{ from } 60 \text{ to } 100, \tag{4.5}$$

$$N \text{ from } 2000 \text{ to } 20000. \tag{4.6}$$

These ranges also happen to be reasonable from the point of view of chemistry. (4.4) says that the number of species of monomer should be in the range from 9 to 11. In modern proteins we have 20 species of amino-acids. It is reasonable to imagine that about 10 of them would provide enough diversity of protein function to get life started. On the other hand, the model definitely fails to work with $a=3$, which would be the required value of a if life had begun with four species of nucleotides polymerizing to make RNA. Nucleotides alone do not provide enough chemical diversity to allow a transition from disorder to order in this model. The quantitative predictions of the model are thus consistent with the Oparin theory from which we started. The model decisively prefers protein to nucleic acid as the stuff from which life arose.

The range (4.5) from 60 to 100 is also reasonable for the discrimination factor of primitive enzymes. A modern polymerase enzyme typically has a discrimination factor of 5000 or 10000. The modern enzyme is a highly specialized structure perfected by three billion years of fine-tuning. It is not to be expected that the original enzymes would have come close to modern standards of performance. On the other hand, simple inorganic catalysts frequently achieve discrimination factors of 50. It is plausible that a simple peptide catalyst with an active site containing four or five amino-acids would have a discrimination

Fig. 13

RANGE OF a, b, N

For good behavior of model. Transition from disorder to order possible with reasonable probability.

$$8 \leq a \leq 10$$

$$60 \leq b \leq 100$$

$$2000 \leq N \leq 20000$$

factor in the range preferred by the model, from 60 to 100.

The size (4.6) of the population in the primitive cell is also plausible. A population of several thousand monomers linked into a few hundred polymers would give a sufficient variety of structures to allow interesting catalytic cycles to exist. A value of N of the order of 10000 is large enough to display the chemical complexity characteristic of life, and still small enough to allow the statistical jump from disorder to order to occur on rare occasions with probabilities which are not impossibly small.

The basic reason for the success of the model is its ability to tolerate high error-rates. It overcomes the error catastrophe by abandoning exact replication. It neither needs nor achieves precise control of its molecular structures. It is this lack of precision which allows a population of 10000 monomers to jump into an ordered state without invoking a miracle. In a model of the origin of life which assumes exact replication from the beginning, with a low tolerance of errors, a jump of a population of N monomers from disorder to order will occur with probability of the order of $(1+a)^{-N}$. If we exclude miracles, a replicating system can arise spontaneously only with N of the order of 100 or less. In contrast, our nonreplicating model can make the transition to order with a population a hundred times larger. The error-rate in the ordered state of our model is typicaly between twenty and thirty percent when the parameters a and b are in the ranges (4.4), (4.5). An error-rate of 25% means that three out of four of the monomers in each polymer are correctly placed. A catalyst with five monomers in its active site has one chance out of four of being completely functional. Such a level of performance is tolerable for a non-replicating system, but would be totally unacceptable in a replicating system. The ability to function with a 25% error-rate is the decisive factor which makes the ordered state in our model statistically accessible, with populations large enough to be biologically interesting.

V.   Consequences of the Model

I will not describe in this lecture the mathematical details of the model. The main result of the mathematical analysis is a formula [Fig. 14]

$$T = \tau \exp (\Delta N), \tag{5.1}$$

for the time T required on the average for a cell to make the transition from disorder to order. Here τ is the average time-interval between mutations at each site, N is the total number of monomers, and Δ is a number which we can calculate, depending only on the parameters a and b. If Δ were of the order of unity, then the exponential in (5.1) would be impossibly large for N greater than 100. We would then be in the situation characteristic of error-intolerant systems, for which the transition to order is astronomically improbable for

Fig. 14   CRITICAL POPULATIONS

Time required for transition from disorder to order

$$T = \tau \exp(\Delta N)$$

τ = mutation time per site
N = population of monomers

$$\Delta = U(\beta) - U(\alpha)$$

Time available for transtion: 10^{10} cells for 10^5 mutation-times, so

$$T/\tau \leq 10^{15}$$

Maximum population for transition

$$N_c \sim \frac{30}{\Delta}$$

(within a facter of 3)

large N. However, when the parameters a and b are in the ranges (4.4) (4.5), which corres-
pond to models with high error-tolerance, it turns out that Δ is not of the order of unity but
lies in the range from 0.001 to 0.015. This is the feature of the model which makes transition
to order possible with populations as large as 20000. Although (5.2) is still an exponentially
increasing function of N, it increases much more slowly than one would naively expect.

According to (5.1) there is a critical population-size N_c such that populaions N of the
order of N_c or smaller will make the disorder-to-order transition with reasonable probabili-
ty, whereas populations much greater than N_c will not. I choose to define N_c by

$$N_c = \frac{30}{\Delta}, \tag{5.2}$$

so that the exponential factor in (5.1) is

$$e^{30} \sim 10^{13} \quad \text{for} \quad N = N_c \tag{5.3}$$

The coefficient 30 in (5.2) is chosen arbitrarily. We do not know how many droplets might
have existed in environments suitable for the origin of life, nor how long such environments
lasted, nor how frequently their molecular constituents mutated. The choice (5.2) means
that we could expect one transition to the ordered state to occur in a thousand mutation-
times among a collection of 10^{10} droplets each containing N_c monomers. It is not absurd to
imagine that 10^{10} droplets may have existed for a suitably long time in an appropriate environ-
ment. On the other hand, if we considered droplets with molecular populations three times

larger, that is to say with $N=3N_c$, then the exponential factor in (5.1) would be 10^{39}, and it is inconceivable that enough droplets could have existed to give a reasonable probability of a transition. The critical population N_c thus defines the upper limit of N for which transition can occur, with a margin of uncertainty which is less than a factor of three. The critical population-sizes given by (5.2) range from 2000 to 20000 when the parameters a and b lie in the ranges 8 to 10 and 60 to 100 respectively.

The properties of our model can be conveniently represented in a two-dimensional diagram [Fig. 15] with the parameter a horizontal and the parameter b vertical. Each point on the diagram corresponds to a particular choice of a and b. Models which satisfy the triple-crossing condition (assumption 9) and possess disordered and ordered states occupy the central region of the diagram, extending up and to the right from the cusp. The cusp at

$$a=e^2=7.4, \quad b=e^4=54.6, \tag{5.4}$$

Fig. 15

VARIETY OF MODELS

CUSP at $a=7.4$
$b=54.6$
Typical cusp catastrophe (Thom)
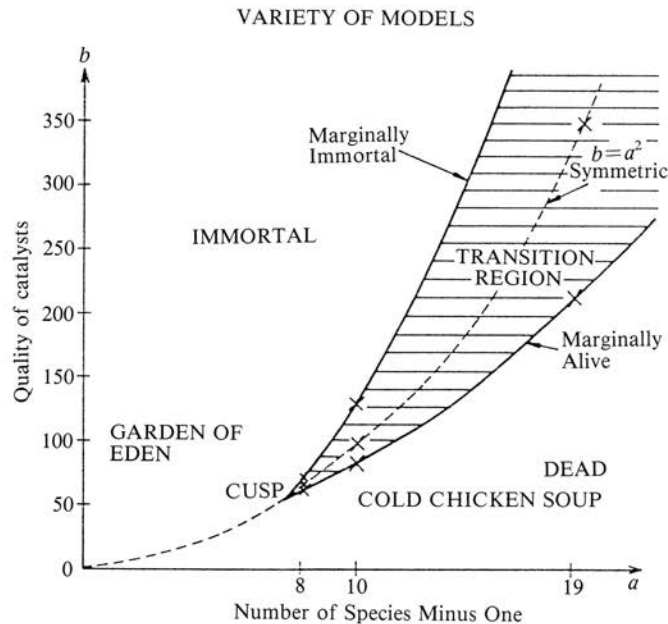
marks the lower bound of the values of a and b for which a disorder-order transition can occur. The critical population-size N_c is large near to the cusp and decreases rapidly as a and b increase. The biologically interesting models are to be found in the part of the central region close to the cusp. These are the models which have high error-rates and can make the disorder-order transition with large populations.

To illustrate the behavior of the model in the interesting region near to the cusp, I pick out one particular case which has the advantage of being easy to calculate exactly. This is the case [Fig. 16]

$$a=8, \quad b=64, \tag{5.5}$$

which has the three equilibrium states

$$\alpha=\frac{1}{3}, \quad \beta=\frac{1}{2}, \quad \gamma=\frac{2}{3}. \tag{5.6}$$

The error-rate in the ordered state is exactly one-third. The value of Δ for this model turns out to be

$$\Delta=\log 3-(19/12)\log 2=0.001129, \tag{5.7}$$

which gives a satisfactorily large critical population-size

$$N_c=26566. \tag{5.8}$$

My friend Christopher Longuet-Higgins, who happens to be a musician as well as a chemist, pointed out that the quantity Δ appearing in (5.7) is well-known to musicians as the frac-

Fig. 16

SPECIAL CASE OF MODEL

$$a=8, \quad b=64.$$

This case is easy to solve exactly. Symmetrical because $b=a^2$. Three equilibrium states:

$$\alpha=\frac{1}{3}, \quad \beta=\frac{1}{2}, \quad \gamma=\frac{2}{3}.$$

Error-rate 1/3 in ordered state.

$$\Delta=\log 3-\frac{19}{12}\log 2=0.001129,$$

equal to differerce between perfect fifth and equitempered fifth in musical scale.
Critical population size

$$N_c=26566.$$

tional difference in pitch between a perfect fifth and an equitempered fifth. On a logarithmic scale of pitch, a perfect fifth is (log 3 — log 2) and an equitempered fifth is seven semitones or (7/12) log 2. The smallness of the difference is the reason why the equi-tempered scale works as well as it does. The smallness of Δ is also the reason why this model of the origin of life worked as well as it does. Old Pythagoras would be pleased if he could see this example, justifying his doctrine of a universal harmony which embraces number, music and science. After this digression into Pythagorean mysticism I return to the general properties of the model shown in Fig. 15.

The region below and to the right of the central strip represents models which have only a disordered state and no ordered state. These models have a too large (too much chemical diversity) and b too small (too weak catalytic activity) to produce an ordered state. Droplets in this region are dead and cannot come to life. I call the region "Cold Chicken Soup" because this phrase has been used to describe the composition of the Earth's ocean in pre-biotic times. The region above and to the left of the central strip represents models which have only an ordered state and no disordered state. These models have a too small (too little chemical diversity) and b too large (too strong catalytic activity) to produce a disordered state. Droplets in this region are frozen into the ordered state and cannot die. I call the region "Garden of Eden" because this phrase has been used to describe an alternative theory of the origin of life. It is possible to imagine cells evolving by random accretion of molecular components so that they drift into the central transition region either from the cold chicken soup or from the Garden of Eden. Once they reach the central region, they are capable of both life and death, and the evolution of biological complexity can begin.

One striking feature of our model which is absent in modern organisms is the symmetry between life and death. In the model, the curve

$$y=\varphi(x)=[1+ab^{-x}]^{-1} \tag{5.9}$$

is invariant under the transformation

$$x\rightarrow 1-x, \quad y\rightarrow 1-y, \quad a\rightarrow(b/a). \tag{5.10}$$

In particular, the model with $b=a^2$ has complete symmetry about the unstable saddle-point at $x=y=1/2$. The ordered state and the disordered state are mirror-images of each other. The probability of a transition from disorder to order is exactly equal to the probability of a transition from order to disorder. In the symmetrical model with $b=a^2$, death and resurrection occur with equal frequency. The origin of life is as commonplace an event as death.

How did it happen that, as life evolved, death continued to be commonplace while resurrection became rare? What happened was that the catalytic processes in the cell became increasingly fine-tuned and increasingly intolerant of error. The curve $y=\varphi(x)$ remained S-

shaped but became more and more unsymmetrical as time went on. The shape of the curve in a modern cell is shown in Fig. 17, to be contrasted with the symmetrical curve in our hypothetical primitive cell shown in Fig. 11. In the primitive cell the three equilibrium states might have been

$$\alpha = 0.2, \quad \beta = 0.5, \quad \gamma = 0.8, \tag{5.11}$$

with an error-rate of 20% in the ordered state. In the modern cell the curve is pushed over far to the right and the equilibrium states are typically
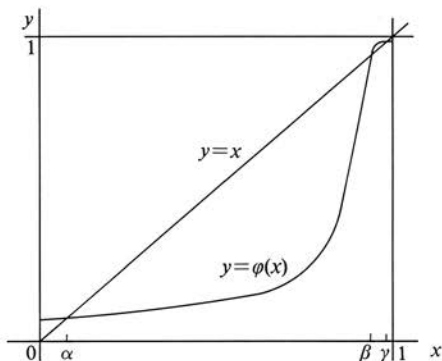
$$\alpha = 0.05, \quad \beta = 0.999, \quad \gamma = 0.9999. \tag{5.12}$$

This position of the ordered state γ means that the error-rate in the metabolic apparatus of a modern cell is about 10^{-4}. The position of the saddle-point β means that an environmental insult such as a dose of X-rays which increases the error-rate to 10^{-3} will disrupt the fine-tuned apparatus and cause the cell to die. Death is easy and resurrection is difficult, because the saddle-point has moved so close to the ordered state and so far from the disordered state. For life to originate spontaneously it was essential to have an ordered state with a high error-

Fig. 17

APPLICATION TO MODERN CELL

Curve $y = \varphi(x)$ highly unsymmetrical

for example

$\alpha = 0.05, \quad \beta = 0.999, \quad \gamma = 0.9999$

Injury with damage $< 10^{-3}$, Recovery, $x \to \gamma$
Injury with damage $> 10^{-3}$, Death, $x \to \alpha$

rate, but when life was once established the whole course of evolution was toward more specialized structures with lower tolerance of errors.

I have said enough, or perhaps too much, about the properties and the consequences of my model. You may have noticed that in talking about the model I have fallen into a trap. I have fallen in love with my model. I begin to talk about it as if it were historic truth. It is of course nothing of the kind. It is not a description of events as they really happened. It is only a toy model, a simple abstract picture which will rapidly be superseded by better models incorporating some of the chemical details which I have ignored.

VI.   Questions and Implications

I have drawn up a list of questions suggested by my model [Fig. 18]. These questions refer not to the model itself but to the implications of the model for the subsequent course of biological evolution. I will comment briefly on each question in turn. After another twenty years of progress in biological research we may perhaps know whether my tentative answers are correct.

1.   Were the first living creatures composed of proteins or nucleic acids or a mixture of the two?

This is the central question in all our thinking about the origin of life. I have already stated my reasons for preferring proteins. I prefer proteins, partly because my model works well with ten species of monomer and works badly with four species, partly because amino-acids fit better than nucleotides the requirements of pre-biotic chemistry, and partly because I am attracted by the Margulis vision of parasitism as a driving force of early evolution and I like to put nucleic acids into the role of primaeval parasites. None of these reasons is scientifically compelling. The question can be answered, in the end, only by chemical experiment

Fig. 18

QUESTIONS

1.   Were the first creatures made of proteins or nucleic acids or a mixture of both?
2.   When did random genetic drift give way to natural selection?
3.   Does the model contradict the Central Dogma of molecular biology?
4.   How did nucleic acids originate?
5.   How did the modern genetic apparatus evolve?
6.   How late was the latest common ancestor of all living species?
7.   Can we find a concrete realization of the model, for example a population of 2000 amino-acids in polypeptides which can catalyse each other's synthesis with 80% accuracy?
8.   Can such a population maintain itself in homeostatic equilibrium?

and paleontological observation.

2.   At what stage did random genetic drift give way to natural selection?

The model has life originating by neutral evolution according to the ideas of Kimura. A population crosses the saddle-point to the ordered state by random genetic drift. The model does not allow natural selection to operate, because it does not allow the island populations to grow or to reproduce. So long as there is no birth and death of cells, there can be no natural selection. However, once a cell has reached the ordered state as defined in the model, it can go beyond the model and pass into a new phase of evolution by assimilating fresh monomers from its environment. A cell which increases its population N by assimilation will quickly become stabilized against reversion to the disordered state, since the life-time of the ordered state increases exponentially with N. It can then continue to grow until some physical disturbance causes it to divide. If it divides into two cells, there is a good chance that both daughter populations contain a sufficient assortment of catalysts to remain in the ordered state. The processes of growth and division can continue until the cells begin to exhaust the supply of nutrient monomers. When the monomers are in short supply, some cells will lose their substance and die. From that point on, evolution will be driven by natural selection.

3.   Does the model contradict the Central Dogma of molecular biology?

The Central Dogma says that genetic information is carried only by nucleic acids and not by proteins. The dogma is true for all contemporary organisms, with the possible exception of the parasites responsible for scrapie and kuru and a few other diseases of the central nervous system of humans and other mammals. Whether or not the scrapie parasite turns out to be a true exception to the dogma, my model implies that the dogma was untrue for the earliest forms of life. According to the model, the first cells passed genetic information to their offspring in the form of enzymes which were probably proteins. There is no logical reason why a population of enzymes mutually catalyzing each other's synthesis should not serve as a carrier of genetic information.

4.   How did nucleic acids originate?

I remarked earlier on the curious fact that nucleic acids are chemical cousins to the ATP molecule which is the chief energy-carrier in the metabolism of modern cells. I like to use this fact to explain the origin of nucleic acids as a disease arising in some primitive cell from a surfeit of ATP. The Margulis picture of evolution converts the nucleic acids from their original status as indigestible by-products of ATP metabolism to disease agents, from disease agents to parasites, from parasites to symbionts, and finally from symbionts to fully integrated organs of the cell.

5.   How did the modern genetic apparatus evolve?

The modern genetic apparatus is enormously fine-tuned and must have evolved over a

long period of time from simpler beginnings. Perhaps some clues to its earlier history will be found when the structure of the modern ribosome is explored and understood in detail. The following sequence of steps [Fig. 19] is a possible pathway to the modern genetic apparatus, beginning from a cell which has RNA established as a self-reproducing cellular parasite but not yet performing a genetic function for the cell. (a) Non-specific binding of RNA to free amino-acids, activating them for easier polymerization. (b) Specific binding of RNA to catalytic sites to give them structural precision. (c) RNA bound to amino-acids becomes transfer RNA. (d) RNA bound to catalytic sites becomes ribosomal RNA. (e) Catalytic sites evolve from special-purpose to general-purpose by using transfer RNA instead of amino-acids for recognition. (f) Recognition unit splits off from ribosomal RNA and becomes messenger RNA. (g) Ribosomal structure becomes unique as the genetic code takes over the function of recognition. This is only one of many possible pathways which might have led to the evolution of the genetic code. The essential point is that all such pathways appear to be long and tortuous. In my opinion, both the metabolic machinery of proteins and the parasitic selfreplication of nucleic acids must have been in place, before the evolution of the elaborate translation apparatus linking the two systems could begin.

6.   How late was the latest common ancestor of all living species?

The universality of the genetic code suggests that the latest common ancestor of all living creatures already possessed a complete genetic apparatus of the modern type. The geological record tells us that cells existed very early, as long as 3 eons ago. It is generally assumed that the earliest cells which are preserved as microfossils already possessed a modern genetic apparatus, but this assumption is not based on concrete evidence. If the Oparin theory of the origin of life is true, cells came before enzymes and enzymes before genes. It is possible that the evolution of the modern genetic apparatus, as described in the discussion of questions 4 and 5, took eons to complete. The ancient microfossils may date from a time before there

Fig. 19

QUESTIONS

Origin of modern genetic apparatus. Possible pathway.
1.   Nucleotides couple to amino-acids to make them more reactive (Katchalsky)
2.   Nucleotides couple to catalysts to give them more precise structure
3.   Nucleotides coupled to amino-acids grow into transfer RNA
4.   Nucleotides coupled to catalysts grow into ribosomal RNA
5.   Transfer RNA becomes specific to particular amino-acids (beginning of code)
6.   Catalysts use transfer RNA instead of amino-acids for recognition
7.   Catalysts become gereral-purpose with a supply of alternative recognition sequences
8.   Recognition sequences split off and become messenger RNA, leaving the ribosome as a gereral-purpose catalyst with unique structure.

were genes and ribosomes. The pace of evolution may have accelerated after the genetic code was established, allowing the development from ancestral procaryote to eucaryotic cells and multicellular organisms to be completed in less time than it took to go from primitive cell to ancestral procaryote. It is therefore possible that the latest common ancestor came late in the history of life, perhaps as late as half-way from the beginning.

7.   Does there exist a chemical realization of my model, for example a population of a few thousand amino-acids forming an association of polypeptides which can catalyze each other's synthesis with 80 percent accuracy? Can such an association of molecules be confined in a droplet and supplied with energy and raw materials in such a way as to maintain itself in a stable homeostatic equilibrium?

These are the crucial questions which only experiment can answer. But before embarking on experiments, it would be wise to explore the territory by studying computer models of molecular populations with realistic chemical reaction-rates. Computer simulations could tell us which chemicals to use in a droplet experiment with some hope of success. Computer simulations are not only cheaper and quicker than real experiments. They are also easier to interpret. The understanding of the origin of life will require a collaboration of many techniques, computer simulations of hypothetical primitive cells, molecular analyses of modern cellular structures, and experiments with chemical populations in real droplets. Each of these techniques will point the way for the others to make progress. Our quest for understanding is based solidly on the work of our distinguished predecessors, Oparin, Schrödinger, Eigen, Orgel, Margulis and Kimura. We have made a good beginning, even if the end is not yet in sight.

In conclusion I would like to ask one more question. What will happen to my little toy model when the problem of the origin of life is finally solved? This question was answered nearly two hundred years ago by my favorite poet, William Blake [Fig. 20]:

"To be an Error and to be Cast out is a part of God's design."

Fig. 20

To be an Error and to be
Cast out is a part
of God's Design

William Blake