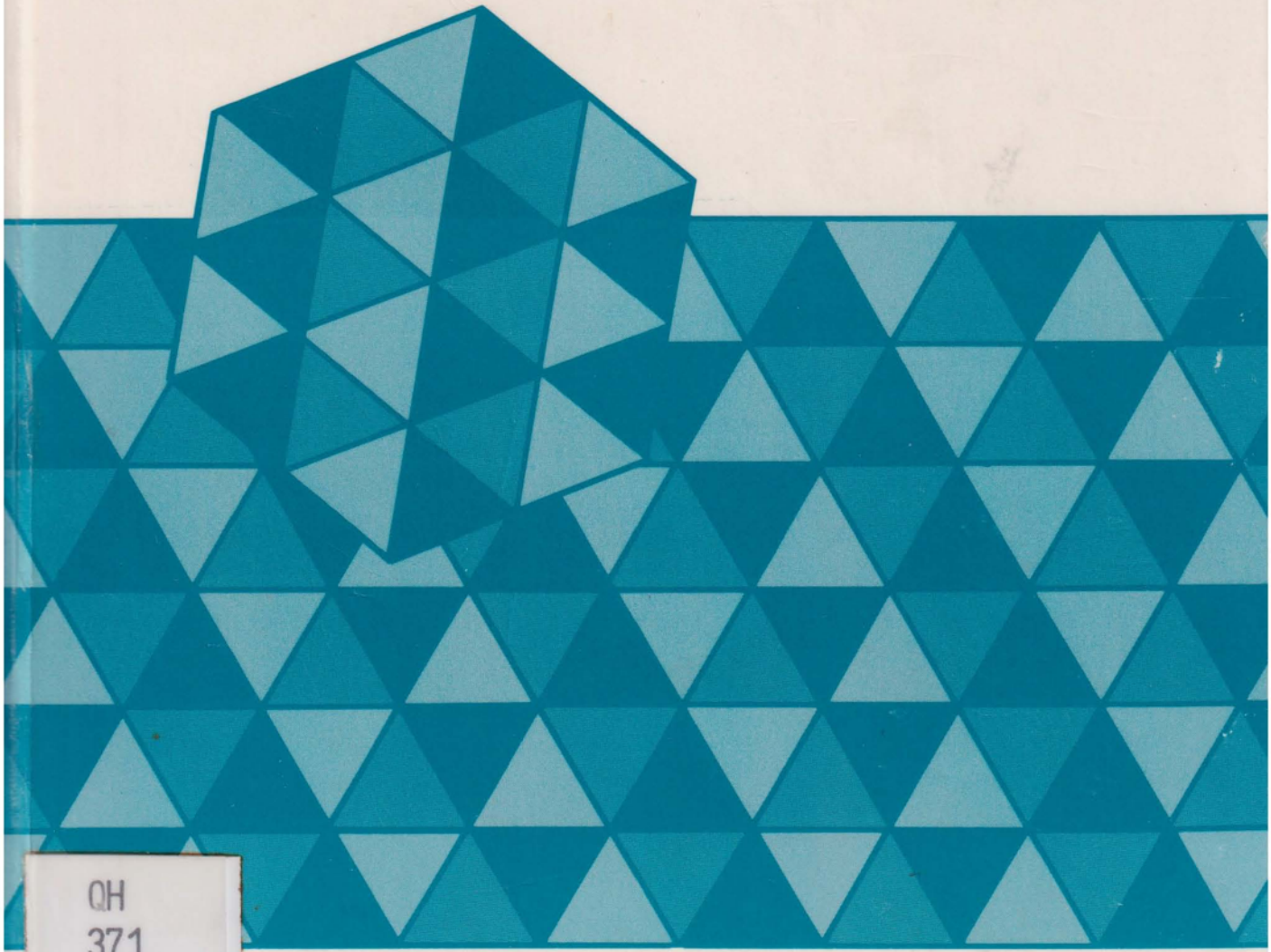
Mathematical Challenges to the Neo-Darwinian Interpretation of Evolution

Editors Paul S. Moorhead Martin M. Kaplan



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MATHEMATICAL CHALLENGES TO THE NEO-DARWINIAN INTERPRETATION OF EVOLUTION

ORGANIZING COMMITTEE

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Alan R. Liss, Inc., is pleased to reprint *Mathematical Challenges to the Neo-Darwinian Interpretation of Evolution* in response to that demand.

MATHEMATICAL CHALLENGES TO THE NEO-DARWINIAN INTERPRETATION OF EVOLUTION

A Symposium held at

THE WISTAR INSTITUTE OF ANATOMY AND BIOLOGY

April 25 and 26, 1966

Edited by

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PREFACE

DR. MARTIN KAPLAN: Perhaps a few words on the genesis of this Symposium would be of interest. Actually, the seed was sown in Geneva in the summer of 1965 during the course of two picnics held at Vicki Weisskopf's house and at my house, on two consecutive Sunday afternoons. Koprowski and I, the only biologists present, were confronted by a rather weird discussion between four mathematicians — Eden, Schützenberger, Weisskopf and Ulam — on mathematical doubts concerning the Darwinian theory of evolution. At the end of several hours of heated debate, the biological contingent proposed that a symposium be arranged to consider the points of dispute more systematically, and with a more powerful array of biologists who could function adequately in the universe of discourse inhabited by mathematicians. It remains to be seen whether the end product of this Symposium will settle any of the issues raised in Switzerland. I suspect that instead of a peaceful accord we shall witness the parallel of other peace conferences now underway in Switzerland. Before proceeding, however, I should like to quote the considered opinions of partners in an eminent mathematical team, Russell and Whitehead.

Russell said, "Mathematics is the only science where one never knows what one is talking about nor whether what is said is true." And Whitehead, "I will not go so far as to say that to construct a history of thought without profound study of the mathematical ideas of successive efforts is like omitting Hamlet from the play which is named after him; that would be claiming too much. But it is certainly analogous to cutting out the part of Ophelia. This simile is singularly exact, for Ophelia is quite essential to the play. She is very charming and a little mad."

— MARTIN KAPLAN

WELCOME TO PARTICIPANTS

DR. HILARY KOPROWSKI, *Director*
The Wistar Institute
Philadelphia, Pennsylvania

Ladies and gentlemen: On April 8, 1781, Mozart wrote to his father that the night before, between eleven and twelve o'clock — in one hour — he had composed a sonata for violin and piano (which subsequently bore the number Köchel 379) and that he had not had time to write the piano part. So, he essentially composed only the part for Violinist Brunetti. The next day, Mozart played the piano himself, accompanying the violinist. The autograph of that sonata is in the Library of Congress, and it bears out completely what Mozart said. The violin part is written in a yellowish ink, and the piano part consists of certain unintelligible shorthand notes. Later on, in a dark inn, Mozart filled in the piano part and, morever, rewrote the entire coda on a new leaf.

Another story concerning a Mozart composition, which may bear directly or indirectly on our meeting, is the history of his Prelude and Fugue (No. K-394) written a year later, where the Prelude follows the Fugue. In the autograph sent to his sister he said, "It is rather clumsily written because while I was writing out the Fugue I was thinking out the Prelude."

I think perhaps these two musical events bear some parallel to our meeting today. Dealing with scientific theories, we either can have the first choice — that a part for one instrument was written and the other part to complete the theory needs either to be written or transcribed, in this case, from an unintelligible shorthand — or the other possibility that the fugue is written but the prelude is to be put in the proper place.

With this, it is my pleasure to welcome you to The Wistar Institute.

REMARKS BY THE CHAIRMAN

SIR PETER MEDAWAR
National Institute for Medical Research
London, England

Thank you very much. Ladies and gentlemen: I want to make just a few introductory remarks. I think it is the distinguishing mark of all true biologists as opposed to mere sectarian specialists that they are deeply interested in the mechanism of evolution. As Dr. Kaplan has explained, the immediate cause of this conference is a pretty widespread sense of dissatisfaction about what has come to be thought of as the accepted evolutionary theory in the English-speaking world, the so-called neo-Darwinian Theory. This dissatisfaction has been expressed from three quarters and is not only scientific. First of all, religious: Where once the complaint was that evolution happened at all, now the complaint generally is that it happens without Divine motivation. Many of you will have read with incredulous horror the kind of pious bunk written by Teilhard de Chardin on this subject, if Professor Schützenberger will excuse my putting it that way.

Then, there are philosophical or methodological objections to evolutionary theory. They have been very well voiced by Professor Karl Popper — that the current neo-Darwinian Theory has the methodological defect of explaining too much. It is too difficult to imagine or envisage an evolutionary episode which could *not* be explained by the formulae of neo-Darwinism.

Finally — and these are really, I think, the only objections that should concern us — there are objections made by fellow scientists who feel that, in the current theory, something is missing; and we look forward to hearing their formulation of what, precisely, is missing.

These objections to current neo-Darwinian theory are very widely held among biologists generally; and we must on no account, I think, make light of them. The very fact that we are having this conference is evidence that we are *not* making light of them.

After these introductory speeches, I will call upon Dr. Loren Eiseley to introduce the conference. I don't know the title of your address, Dr. Eiseley. Perhaps it hasn't got one, but come and give it, nevertheless.

INTRODUCTION TO THE CONFERENCE

DR. LOREN C. EISELEY
University Professor of Anthropology and the History of Science
University of Pennsylvania
Philadelphia, Pennsylvania

Since we began with a reference to music, I would like to make a comment upon painting before we proceed to other serious subjects. Some of you may be aware that Camille Corot, the famous nineteenth century French landscape painter, had a habit of going out in the early morning and painting while there was a veil of mist upon the landscape. When the sun came out, things dried up and the land took on a very clear shape and form under the midday sun. Corot would then put away his painting materials and remark, "There is nothing more to be done now. One can see too clearly."

I think what he was talking about, at least in terms of the school of thought of his time, was that when one sees things exposed in a certain terrible clarity, one perhaps sees too much. Mystery, and the elusive shadows that are also part of the landscape, disappear. Something goes out of it; and I think perhaps there is a little parable here in connection with our problems of evolution and neo-Darwinism.

If one is merely seeking, as I am sure we are, the essential truths as to the nature of evolution, the nature of the process, I think it is well to consider Corot's remarks. Indeed perhaps there is something about the neo-Darwinian approach and certain of its successes that has led us to assume that all of the mist and the shadows have departed and that everything is revealed under the midday sun. Perhaps it will do us no harm here for a little while in this gathering to consider the fact that it is sometimes easy to assume, when the veil grows thin, that we have the total and complete answer to all our questions.

My distinguished colleague, Thomas Kuhn, with whom some of you may be acquainted, has had a good deal to say in late years about scientific models or paradigms in the history of science, and the way in which those paradigms influence the thinking of a particular period. What he says is something like this: (and it has a relationship to Corot's landscape) that discoveries are not made unless the paradigm, the model, finally extends outward, beyond what it was originally intended to encompass. Along that frontier there begins to appear this

nebulous area, this veil over the landscape which leads men, not necessarily to immediate answers but to questions, to new experiments, to some groping realization that perhaps what they thought was settled for all time is not settled, or is incomplete.

If we were to step back for a moment into the nineteenth century, we might bear in mind that immediately prior to Darwin's pronouncement in "The Origin of Species" and his emphasis on fortuitous variation and selection as part of the process of evolutionary change, there was a kind of catastrophic conception of geology, indeed an assumption that these separate geological periods of the past were shut away from each other, as if by a series of closed doors. There existed, however, a thread of spiritual continuity, a kind of eternal blueprint, in the mind of the Creator; so that the succeeding forms, although different, bore an anatomical relationship but not a physical relationship to what had preceded. This idea, which of course has been long exploded, nevertheless constituted one paradigm, a genuine attempt to explain new discoveries in the field of paleontology and geology which at the same time were beginning to fall into conflict with the theology of the time.

There was another view more immediately related to the conception of natural selection expressed in the eighteenth century phrase of John Hunter—"natural government." This, in contrast to the other paradigm, was essentially an expression of the Newtonian idea that a balanced world machine extended over into the domain of biology. A certain degree of variation was beginning to be recognized for a variety of reasons that we need not bother to go into here. "Natural government," however, implied a degree of potential variability in animal organisms which was always and constantly held in balance and in check by the struggle for existence.

All of this went under names other than natural selection. Terms like "pruning," "policing," "pre-occupation principle" and "localizing principle" were current. With the semantic shift which took place with the introduction of the phrase "natural selection," men tended to forget this earlier vocabulary. We forget that one face, the conservative face of natural selection, was recognized before Darwin. It is worth noting that in the reading I have given to this period, I have encountered just one reviewer after Darwin, about 1862, who realized the connection between this liberalizing force expressed by Darwin and the conservative aspect of natural selection expressed by his predecessors. The reviewer, interestingly, hauled up and said in effect, "Isn't it

strange that what Darwin has expressed in the *Origin* can fit equally well this past conception of natural government; or, on the other hand, the idea of animal life as involved in persistent organic change?"

I have now given models of thought fitting their time and place, not without facts to back them, answering to a particular intellectual climate. At the same time in the very extension of knowledge at the paradigm's border itself, the new questions finally begin to be asked and as a consequence the world changes.

This is why I say that using the parable of Corot's thinking, we should give serious thought to the question of whether we have reached a certain point of hesitation in our seemingly clear explanation of the way evolution comes about. Have we really answered all the questions; or is there something peculiarly attractive, almost like a Kipling "Just So" story, about natural selection? The range of ideas and the possibilities which they cover are so extensive that it is in a sense a bit deceptive. Perhaps, after all, there is still a veil of mist hanging over this seemingly sharp, clearly defined landscape.

I would merely add one other comment here before we turn to the problems of the Symposium (and I say it with no wish to inject theological arguments into this gathering): I did know Father Teilhard. I knew him as a very great gentleman. I do not happen to agree with all of his ideas. On the other hand, I have a high respect for him as a man. I would like to add in this connection that I think we forget at times that even almost to the end, Charles Darwin was also troubled, I suspect, in the back of his mind by some of these very problems that still concern us. He used to say that the intricacies of the human eye gave him cold shudders.

In connection with some of these obscure problems of related mutations, or variations that have to be related almost from the beginning in order to be effective, he was not as confident in some of his expressions as the neo-Darwinists. You will remember that here and there he speaks of, and rather slides by, some of these more remarkable problems with a comment that they have reference to mysterious and not understood laws of correlation, which he does not attempt to define. So even in terms of the master thinker, what is meant by the word "fortuitous" in terms of pure chance and what is meant by such expressions as "mysterious laws" we might well make some allowance for. I say this with all due recognition that some of the genetic information now available to us was not available to him. I still think

Darwin expressed a certain tolerance, a marked degree of wary unease, as to whether, indeed, the phrase "fortuitous variation" was a sufficient answer to all our problems.

I think one of the things we will have to be wary of today, which Dr. Medawar in a sense dwelt upon, in our attempt to analyze the pros and cons of whether a neo-Darwinian position satisfactorily accounts for all aspects of evolution or not, is to avoid getting this tangled up with a theological debate, vitalism versus mechanism. The point, it seems to me, no longer lies here so much as it does over in another domain of the organismic approach, the problem of whether there are some aspects of life, and of chemistry under the control of life, which are not as yet totally accountable for with the means at our command. To say this is not to run off into mysticism. It is to be examining an unknown, just as Darwin in his time was examining an unknown. If we keep this in mind I think that we are less apt to be emotional over some lingering and archaic fear that we will be precipitating ourselves into outmoded nineteenth century controversies.

Not long ago I received for comment a book praising the achievements of science. The author said, in essence, "It is the duty of the historian to hold up all scientific men of achievement as saints for the benefit of oncoming students of science."

What an ironic reversal, in a sense, of our whole conception of what science ought to be, compared with its struggles in the nineteenth century! Now we hold the platform; but let us not engage, either as historians or scientists, in either regarding ourselves as saints or failing to recognize that over the apparently hard, empirical landscape across which we gaze there may still lie some morning haze, some shadows, which we may hopefully illuminate.

The Chairman, DR. MEDAWAR: Thank you very much, Dr. Eiseley. I think we will all agree that Dr. Eiseley has defined the area within which our discussions ought to take place if, in fact, we are going to get anywhere at all.

Inadequacies of Neo-Darwinian Evolution as a Scientific Theory

DR. MURRAY EDEN
Professor of Electrical Engineering
M.I.T., Cambridge, Massachusetts

It seems to me worthwhile to begin my talk by offering a summary of the position I wish to present.

In the first place, Darwinism provided the program for a theory which made plausible an explanation of species without recourse to a *deus ex machina*. The notion that speciation is a continuous process governed by natural law was an attractive one to scientists. Certainly the continuity of evolutionary process has been amply demonstrated by the uses made of it in paleontology, taxonomy, in ecology and in natural history generally. However, the continuity of evolution does not demonstrate that natural laws are operative, for the laws are not known. It is as if some pre-Newtonian cosmologist had proposed a theory of planetary motion which supposed that natural force of unknown origin held the planets to their courses. The supposition is right enough and the idea of a force between two celestial bodies is a very useful one, but it is hardly a theory. It became a scientific theory only after Newton made explicit the description of the concepts of force, velocity, angular acceleration and the like and provided a quantitative description of planetary trajectories.

The notion of natural selection depends upon the empirically verifiable observation that offspring on the average resemble their parents more closely than they do the other members of the population, that individuals are not all the same; that all environments are not the same. Concepts such as natural selection by the survival of the fittest are tautologous; that is, they simply restate the fact that only the properties of organisms which survive to produce offspring, or to produce more offspring than their cohorts, will appear in succeeding generations.

The notion that the germ cells prescribe the properties of the phenotype which develop in a given environment would be true both for a Darwinian and a Lamarckian theory. Current knowledge suggests that the germ cell can be modified while still in the phenotype parent but the means of modification are of a special character, and nowadays the effects of the modifications are not predictable. So this modern genetic theory bears somewhat the same relation to the older theories of heritability that modern nuclear theory bears to classical atomic theory; the atom can be decomposed, but atomic theory still has its uses.

Any principal criticism of current thoughts on evolutionary theory is directed to the strong use of the notion of "randomness" in selection. The process of speciation by a mechanism of random variation of properties in offspring is usually too imprecisely defined to be tested. When it is precisely defined it is highly implausible. The issue of plausibility is central to my argument; namely that when reasonable assumptions are made concerning certain natural processes, together with the assumption of certain specific kinds of randomness in the variation of heritable properties, then other phenomena which are empirically observable appear to be highly unlikely events. As the Jansenist logician Arnauld of Porte Royale put it: "In some cases the likelihood of success is so slight that no matter how great the advantage or how small the expense, good sense advises against risking a wager. It would be sheer folly to bet even

ten coppers against 10,000 gold pieces that a child arranging at random a printer's supply of letters would compose the first twenty lines of Virgil's Aeneid."

I shall not dwell on the first two issues. They are hardly controversial.[1] However it may be worth mentioning that the mechanism of heredity by gene action is insufficient to explain observations which can be attributed to cytoplasmic factors; also the experiments of Sonneborn *et al.* (1) on paramecia appear to demonstrate a Lamarckian kind of inheritance.

In addition there is a recent report of work by J. Brun at Lyon (2) who has found that the nematode *Caenorhabditis elegans* can adapt to quite elevated temperatures if the nematode is given about 8 to 10 generations to adapt to each ½° step. Since the nematode is self-fertilizing, selection presumably cannot be invoked to explain a progressive adaptation. The major issue is the randomness of variation in phenotypic properties and in the precise definition of the space of these properties. It is hardly novel to point out that for very many properties precise definitions are exceedingly difficult to make. However modern genetics offers at least a few clues as to the relation of the space of genotypes to that of the phenotypes, and hence it provides a vehicle for making explicit definitions of random variation. Whether the current genetic dogma is correct or not is another matter.

The Chairman, DR. MEDAWAR: Do you mind my interrupting? For the sake of intelligibility, would you explain to the audience the sense in which you are using the term "space"? It is familiar enough to mathematicians but many of us may not understand it.

DR. EDEN: I am using "space" in two somewhat different but related senses. In the first place, I compute the cardinality of a certain set, that is the number of its elements. In the case of proteins, for example, the space of all proteins is used to refer to the totality of different sequences. I can write a chain of 250 amino acid residues in 20 letters, starting, let us say, with a chain of 250 glycine residues and ending with a chain of 250 valine residues. That is one meaning.

In addition, I would like to associate a metric with certain properties relevant to the problem of distinguishing one population of organisms from another. The totality of these measures I call a space. In other words, I can identify some point in this space with some organism according to the values of the properties I have chosen as coordinates in this space. This is the other use I have made of the word "space". When referring to the phenotype space, I believe I am using the term in essentially the same way it is used by population geneticists today.

I would like to say something about the phenotype spaces. Although I do have some biological competence, it is not in those fields which are closest to evolution, so I must tread with caution. It seems quite reasonable today to accept the postulates that there is a gene associated with each enzyme, that the genes are arranged in a linear string (except perhaps for some bacteria in which it is ring-shaped), that the linear string consists of a sequence of nucleotides, that there is a mapping from the nucleotide string to the amino acid string corresponding to some protein. For the sake of definiteness I will also assume that the correct mapping is that described by Nirenberg and his co-workers (3), although that is not essential to the main argument.

I would like first to make a few simple numerical computations which bear on the issue of plausibility that certain events can arise from random variation. I shall define a random variation by prescribing that every possible elementary variation is equally probable. Geneticists may object that the frequency of occurrence of point mutations is by no means uniform over the space of all possible point mutations. However, there is to my knowledge, no way of predicting the distribution of mutation frequency for an arbitrary organism so there is no reason to make any other assumption. Dr. Mayr has given as the definition of randomness of mutation, "It merely means a) that the locus of the next mutation cannot be pre-

[1] This assumption of general agreement was an error on my part as the discussion on this point indicates. However, the notion that neo-Darwinian evolutionary theory is incapable of disproof is not a novel one with me.

dicted, and b) that there is no known correlation between a particular set of environmental conditions and a given mutation. It does not bring into question the facts that the probability of mutation is much higher at some loci than at others and that the number of possible mutations at any given locus is severely limited by the other mutational sites of the cistron and indeed by the total epigenotype" (4). Of course, the narrower the distribution for the probability of mutation, the less the justification for using the word "random", at least in the first sense, so that one may with equal validity see the process as essentially deterministic with the superposition of some "noise". If, in truth, mutational distributions are of this character, then in a probabilistic sense one can predict the next mutation. I may not understand Dr. Mayr's second point. It seems to me that one of the virtues of modern work in evolution is that it has gotten as far as it has in the face of such difficulties, so that it also seems to me of dubious value to raise the current state of ignorance to the status of a principle. It is my impression that studies on mutagens may well shed some light on this latter point.

Let us consider first the space of polypeptide chains of length 250 or less. We may think of words which are 250 letters long, constructed from an alphabet of 20 different letters. There are about 20^{250} such words or about 10^{325}. Let us compare this with certain other quantities, for example the number of protein molecules that could ever have existed on earth in organisms. Assume a biosphere of cells 1 cm. thick over the surface of the earth, a protein concentration in these cells of 30%, a density of 1, an age for life on earth of 10 billion years and an average lifetime of a protein molecule of 1 second. Of course all these quantities except density err very heavily toward the high side. The number of protein molecules that ever existed is by this computation about 10^{52}. Clearly the number of species of protein molecules is much smaller than this, say 10^{40}, but it would be immaterial to our purposes to try to make such a reduction. It is obvious that 10^{52} is such an infinitesimal number when compared with 10^{325} that we would be understating the case badly to say the space of protein molecules has barely been scratched. Yet this relatively small set of 10^{52} proteins contains within it all the useful proteins which have existed to date.

Two hypotheses suggest themselves. Either functionally useful proteins are very common in this space so that almost any polypeptide one is likely to find has a useful function to perform or else the topology appropriate to this protein space is an important feature of the exploration; that is, there exist certain strong regularities for finding useful paths through this space.

We cannot now discard the first hypothesis but there is certain evidence which seems to be against it. If almost all polypeptide chains were useful proteins we would expect that existing protein would exhibit very different distributions of amino acid residues. It is possible to find pairs of proteins which differ very markedly in distribution, but for the great bulk of known proteins, the assumption that they are samples drawn from the same population, as demonstrated by a simple chi-square test, is very plausible.

More specifically we may consider the α and β chains of human hemoglobin A (5). They contain 140 and 146 residues respectively. When the chains are arranged for optimal homology it is found that they agree in 61 places, there are 9 "gaps" and 76 places in which they differ. It is quite plausible to assume that one was derived from the other or both from a common precursor. If the Nirenberg mapping is accepted as correct, then 42 places required a minimal nucleotide change of one, 33 required two changes and one required three changes. Thus, at the least, the chain of events leading from α to β required a minimum of 111 point mutations, exclusive of deletions and additions, or 120 if we wish to include the "gaps". Yet if we look at the distributions of residues, they are quite similar, with a mean difference of about 1½ per amino acid type.[2] Certainly the

[2] The discussion as to whether point mutation or deletion and insertion was the correct mechanism for change in hemoglobin is irrelevant to the argument given here. In either case one would not anticipate that the distribution for the amino acids occurring in the α but not the β chain is very close to the distribution of residues occurring in the β but not the α chain.

coding constraints would not imply so good an agreement. Finally it may be noted that the distribution for those places which the two polypeptide chains have in common is rather different from either of the distributions of places in which the chains differ.

Dr. Wright has implied in his comment on my working paper that he regards the size of the protein space as largely irrelevant. He points out that the game of twenty questions can identify one point in a very large space of answers without bothering to examine most of the space. Of course, he is correct, but I believe he has misunderstood my argument.

Simply stated, there are some paths which lead fairly directly from one point to another in this space but there are many more paths of very much greater length between the same two points. The actual path-lengths traversed are limited by the number of generations in the organism's history so that the long paths are inaccessible, only the short ones can have been taken.[3]

I can illustrate this by another numbers game on the α and β chains of hemoglobin. Assume that 120 point-mutations lead between α and β by a unique path. By the Nirenberg code the average number of amino acids that can be reached in a single step (call this "of distance 1") is between 8 and 9.

Further assume a uniform distribution of point mutations anywhere in the length of 420 nucleotides, a mutation rate of 10^{-6}, and an average population size of 10^6. It is essential to the calculation that each step in this path correspond to a position on the fitness surface higher than all positions of distance 1 from it. Note therefore that we need to compute the expected time for 1 step to be taken and then multiply it by only 120. We must also make an assumption concerning the extent of selection pressure for each step. With the strongest possible selection pressure it would require 20 generations to convert the population from one level to another. On this basis we would expect on the order of 2,700,000 generations to be required for one hemoglobin chain to transform to the other. This is a little large but not implausible. We could reduce the estimate by changing the assumptions somewhat. However, the central point is that it is exceedingly unlikely that the trajectory on the fitness surface followed the shortest path. It is much more plausible to assume that the path meandered over the fitness surface seeking a higher level at every step, following neither the path of steepest ascent nor the shortest path. How long would the path be if we assumed some kind of "randomness" in the fitness surface? The mathematical problem appears to me to be a difficult one and I have no estimate to offer except that it clearly is many powers of 10 greater than the minimal distance of 120.[4]

Much of modern molecular genetics concerns itself with the mapping of phage and bacterial chromosomes. One of the striking results of bacterial genetics is the discovery that genes are organized into larger units under the control of an operator, with the genes linearly arranged in the order in which the enzymes to which they give rise are utilized in a particular metabolic pathway. Such arrangements, for which there is strong evidence, include the lac, his, try and cys operons. The fact that "supergenes" found in the chromosomes of metazoa are very difficult to decompose by recombination suggest that there may be some such order in the more complex forms of life as well.

So far as *E. coli* is concerned we might ask what is the probability that a rearrangement of unordered genes will organize certain sub-groups into operon clusters. Cuzin

[3] Dr. Wright has also taken issue with my related analogy to the writing of a library of books. I note that Dr. John Kendrew in his recent popular account of modern molecular biology, "The Thread of Life", uses the identical model. He writes: "It may be surprising that a random process like this can improve a species or even produce a new species, indeed lead eventually to the whole vast diversity of animal and plant life we see around us. But it must be remembered that these processes have operated over an enormous span of time, more than five hundred million years."

In this instance Dr. Kendrew has been misled by the attractive irrelevancy of the length of time available. Five hundred million years may be long in human terms; it is the blink of an eye in eternity. The length of time is relevant only when the probabilistic structure of events and changes occurring in this time are also known.

[4] If one assumes that insertion and deletion was the principal mechanism rather than point mutation, the computation given here is irrelevant. However, a new set of difficulties is substituted. Since more than one amino acid residue may be altered at each step, the path from one hemoglobin to the other hops over the protein space in wilder jumps, and yet at each successful jump the hemoglobin must have been biologically valuable. If the frequency of genetic modification is high and the density of useful hemoglobins in the protein space is also high, then one must explain why there are so few variants occurring in the blood of the species in question.

and Jacob in Paris (6) and Beckwith and Signer at Harvard (7) have demonstrated that it is indeed possible to transpose segments of the bacterial chromosomes from one place to another by procedures that might well have occurred in nature.

If I understand the rather complicated procedure correctly, it involves two or more transfers of genetic material, an event of the frequency of a recombination, say 10^{-3} and two events which exhibit the frequency of mutations, say 10^{-6}.

Now in the experimental situation the geneticist can select for each stage in the process and need not wait for the occurrence of very rare events. However, each step in this chain, while it can occur in nature, does not of itself confer any selective advantage to the phenotype so that the individual steps are independent. To make a very rough estimate, a transposition of chromosomal material should occur in an unselected environment with a frequency of 10^{-15} for each sequential pair of genetic transfers.

Now the workers mentioned above have shown that the transposed segments are arbitrary lengths of genetic material. Thus on the assumption that the ring chromosome of *E. coli* opens at the uniquely appropriate place and that the episome provides the precise gene next in metabolic order, the probability of such an event, assuming a uniform distribution on chain segmenting, is 10^{-21}. Then to achieve a single ordered pair of genes on these assumptions would require something like 10^{36} genetic transfers. Sexual genetic transfer in *E. coli* takes about two hours and there are only about 10^{12} such periods dating from the beginning of life to now. Finally, genetic transfer between bacteria is a rare event. I have been unable to find estimates in the literature but I will assume that at any instant in time 10^{-6} of the bacterial populations are "mating". Thus one would need an average population of *E. coli* of 10^{30} (about 10^{13} tons or a layer on the surface of the earth two centimeters thick) if one expected to find a single ordered gene pair in 5 billion years.

I am well aware that such estimates are fraught with danger. A change in one of the biological parameters, a discovery of a new transposition mechanism can make such speculations an exercise in futility, but the point is that such estimates can only be overthrown by the finding of a new *determinate* feature.

As a matter of fact such a mechanism seems to operate in recombination, which after all involves the breakage of two pairs of DNA strands and a transposition of their pieces. Homologous sections obviously "recognize" each other (an essential and surprising fact that would seem to require a physical explanation), but there is no reason to assume that the ends of the recombinant fit. However, there is a way out, and I wish to thank Dr. Maurice Fox for calling this possibility to my attention. Since each recombinant strand is associated with a complementary one, the Kornberg enzyme can repair any gaps by "reading" the complementary strand. Without such a biological and deterministic mechanism the process of recombination would almost always lead to nonsense.

As a last numerical exercise, consider the following: The human genetic complement comprises about 10^9 nucleotides or about one nucleotide for each year since life appeared on earth. Because at some time or other there were no nucleotides, the average rate of accrual is about one nucleotide per year. Dr. Wright has objected that evolution should be reserved for biological phenomena and not for pre-biology, and I certainly agree with him. However, in this example I am not at all referring to prebiology. It is immaterial whether we start with 1 nucleotide, 100 or indeed the 10^7 nucleotides of a bacterium. To increase from 10^7 to 10^9 instead of from 1 to 10^9 means the addition of 99×10^7 nucleotides instead of $100 \times 10^7 - 1$ nucleotides, not a great difference. If Dr. Wright is proposing that the notions of a naturalistic evolution are further restricted only to genetic events in which the change in total genetic length is negligible and perhaps incidental to the process of speciation, then indeed what I have said is irrelevant. Nevertheless it seems to me that most striking use has been made of evolution in studies of phylogeny; and if the chromosomes of the organisms of 2

and 3 billion years ago were as large and complicated as our own, so that the problem of assembling a meaningful ordered sequence of 10^9 nucleotides is pushed back in time to pre-biology, then the explanation not only of the origin of life, but also of the complexity of life is to be found entirely in physics or chemistry.

It may be that the formation of the nucleotides and amino acids are not biological questions, nor perhaps the formation of the first replicating entities, or the DNA, RNA, -messenger RNA, -amino acid code, but surely it is a biological and presumably evolutionary question to ask how new enzymes are created, new functions developed, how the complex may derive from the simple, or how a line of life may accumulate information.

I would like now to return to the description of the space of phenotypes. First, it is my understanding that the variations in phenotype induced by point mutations or deletions are frequently discrete and not continuous; eye and skin pigments, hair and vein patterns change drastically, enzyme function is markedly diminished or regulation changed. In the phenomenon of polymorphism and speciation generally, it is plausible to assume that recombination is much more important than mutations. Here too, the polymorphic manifestations frequently do not blend into a continuous scale. In other words, some values may simply not be accessible. There are two important consequences. First of all, discreteness drastically decreases the space of phenotypes; random variation takes on a more restricted meaning. Second, it leaves us with the problem of discovering which points are accessible without reference to selection, and why.

Mimetic phenomena have been widely discussed by natural historians. Consider the two-toned pink orchid and the two-toned pink praying mantis which is its mime. Here the mimesis is both in terms of form and of color. I am informed by Dr. Lettvin that the colors are metamers, that is, that the spectral distributions of the two pigments (animal and vegetable) are different but that they have the same hue and saturation to our eyes. It can hardly be that the mimesis was designed for human eyes; nor does this phenomenon seem to be an accident, because we are aware of many color mimetic pairs. It may be that a solution to this anthropomorphic view is that the *perceptual* color space is common to all organisms, as are the visual pigments of light-sensitive sense organs. This does not tell us how to define the two phenotype spaces which so resemble each other along certain coordinates, but it does suggest a reduction in the number of points needed in this space.

Finally, a word should be said about behavior. Much behavior is innate. Even those parts of behavior which are adapted through learning presuppose an innate mechanism for deciding what behavior is "good" and what is "bad" for the organism, as well as a mechanism for making inductive inference by correlating the organism's behavior with the organization of its perceptual world. Behavior is one of the key isolating mechanisms for populations and is modifiable by evolution. The ethologists have begun to provide structural models for certain aspects of behavior; but, in the main, behavioral dimensions are very ill-defined. We can merely say that it seems plausible to believe that very strong constraints exist as to the character and extent of behavioral variation.

Dr. Conant once commented that an incomplete theory is not discarded until a better one has been proposed. I cannot presume to satisfy that prescription. Nevertheless I would suggest that there are principles of organization to look for concerning which we are beginning to accumulate evidence. The helical non-integral screw symmetries in proteins and nucleic acids are repeated in larger structures such as the helical cylinder of tobacco mosaic virus protein, a protein that will organize itself into this structure even in the absence of the RNA core. In appropriate and unexceptionable aqueous media these structures are thermodynamically highly stable. A recent report in *Science* by Morgan and Uzman (8) described the packing of ribosomal particles of about 180 Å° diameter in the chromatoid body of *Entamoeba invadens* into long helical arrays. There is no physical principle known to me that predicts a very

high stability for helices, but the pervasiveness of helical structures suggests that such a principle is worth looking for.[5]

There is also great thermodynamic stability to be found in the tertiary structure of many enzymes. There is a high likelihood that complementary strands of DNA will "recognize" each other and form a double helix in correct register with no other biological material to mediate this recognition. The long range periodicities in reconstituted collagen and the synthetic formation of myosin fibrils suggest that physical or chemical explanations are appropriate.

I would also like to suggest that an opposite way to look at the genotype is as a generative algorithm and not as a blue-print; a sort of carefully spelled out and foolproof recipe for producing a living organism of the right kind if the environment in which it develops is a proper one. Assuming this to be so, the algorithm *must* be written in some abstract language. Molecular biology may well have provided us with the alphabet of this language, but it is a long step from the alphabet to understanding a language. Nevertheless a language has to have rules, and these are the strongest constraints on the set of possible messages. No currently existing formal language can tolerate random changes in the symbol sequences which express its sentences. Meaning is almost invariably destroyed. Any changes must be syntactically lawful ones. I would conjecture that what one might call "genetic grammaticality" has a deterministic explanation and does not owe its stability to selection pressure acting on random variation.

One concluding comment on randomness: Certainly organisms contain many built-in as well as learned ways for trying to survive. Many also have ways for enhancing the survival of offspring. Both tasks require interpreting information from the environment so that the genotype must specify that the phenotype be motivated to interpret the environment to this purpose.

The question as to whether the genotype receives information about its environment and modifies itself so as to improve the survivorship of the phenotype to which it may give rise, is answered "No" by evolutionists. I do not take issue with the empirical evidence in favor of this position. However a "Yes" answer does not require that one adopt a mystical or teleological principle. After all, computer programs can be written to do precisely this and sometimes so-called adaptive programs work very well.

I might tell you an anecdote in this regard. There is a good deal of work that has been done on game-playing with computers; and perhaps the most successful work has been done by Samuel on playing checkers. In the course of this work, what was required was to play many checker games, a person against the computer, which involved taking up a lot of human time, let alone computer time. Dr. Samuel, at IBM, had at his disposal a large number of computers; so rather than play against the computer himself, he had one computer play against the other computer and accumulated much more experience this way. However, there was a certain problem. For reasons best known to the computers, they made a decision at one time to lose the game rather than to win the game; and this is as difficult a task as winning the game. So the point is that what looks to us as motivation, what looks to us as teleology, need not be. Again, from the point of view of the computer, it certainly is not; the computer has no motivation.

On the other hand, every attempt to provide for "computer" learning by random variation in some aspect of the program and by selection has been spectacularly unsuccessful, even though the number of variants a computer can try can easily run into billions. Of course, the simple explanation may be that the computer programmers weren't smart enough to set up the problem right. It seems to me that an adequate theory of adaptive evolution would supply the computer programmer with the correct set of ground rules and perhaps some day it will.

[5] I was in error here. I should have known better. As Dr. Weisskopf pointed out to me, the occurrence of helices can be predicted on thermodynamic grounds. Briefly stated, a linear array of elements with regular attachment sites and with sufficient degrees of freedom at these sites will under predictable environmental conditions exhibit a surface free energy minimum in a helical configuration.

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Discussion

PAPER BY DR. EDEN

The Chairman, DR. MEDAWAR: Gentlemen, I would like to throw Dr. Eden's paper open for discussion, and there certainly is a very great deal in it to discuss.

I should like to open the discussion by questioning him on one particular point, namely, his allegation that the principles of evolution by natural selection are tautologous and, therefore, vacuous. I think that is mistaken. I would like to go through the points with Dr. Eden, if he wouldn't mind.

Supposing we start with the assumption, which is certainly true, that all the human beings alive in two hundred years' time will be descendants of human beings alive today. I don't think this can seriously be questioned. As I see it, the theory of evolution by natural selection would make the following two statements, neither of which is tautologous. The first is that human beings alive today will not take an equal share of being counted among the ancestors of the human beings alive in two hundred years' time. That is not a tautologous statement. For we might take a share of the ancestry of future populations that was strictly proportional to our numbers, but we don't. Some people will make a greater contribution than others. That is the first point.

The second point is that these inequalities in the contribution people make to the population of the future will be related to their genetic makeup. That is also not a tautology. That is all, so far as I know, that is contained in the theory of evolution by natural selection.

It is true that expressions like "survival of the fittest," which belong to a very elementary level of discussion, are tautologous; but we aren't really talking at this level. I would like Dr. Eden to say, are those two statements of mine tautologous?

DR. EDEN: No, certainly not. You misunderstood which statements I regard to be tautologous. Perhaps "tautology" is the wrong word. Perhaps I should say "definition." There are two empirically verifiable facts. No. 1, taken in the crudest sense, is that offspring resemble their parents. If you wish, you can put it in somewhat more modern terms in the sense that offspring represent the outcomes of the germ plasm of their parents. That is certainly an empirically verifiable observation.

The other observation is that there are events in life which cause certain organisms to live and certain organisms to die; and which organism dies before it produces offspring is a function of certain parameters of the world in which it lives. To that extent, it is fit or unfit to live in that environment. Of course, only those which survive long enough can produce offspring and some produce more offspring than others.

Those are the two empirically verifiable statements and I believe that my second statement corresponds to the two statements that you made. Beyond that, there is nothing to be said about natural selection. There are no other rules; and that is why I used the analogy of the cosmologist, namely, there must be some rule of evolutionary behavior that can be tested. We can make certain observations that are empirical and, hence, we should look for those rules that can in principle be falsified by observation. This essentially what I have been trying to say. I do not believe that simply stating these two empirical events baldly is sufficient to claim that it is a theory. It is simply a redefinition.

The Chairman, DR. MEDAWAR: I think it is a theory. It couldn't be otherwise.

DR. ERNST MAYR: I just want to say that although these two statements are perfectly correct, they are both rather irrelevant to the theory of natural selection. The fact that offspring are similar to the parents in some ways is perfectly true but it has nothing to do with natural selection. The question is, which of the offspring will, in turn, have the greatest probability of having offspring? This is the core of the theory of natural selection, which does not depend on an individual's resemblance to its parents but on its own genotype or phenotype, which controls the probability of this individual leaving offspring. This is what the population geneticists define as fitness.

As to your second theory—that there are factors in the environment which control fitness, which contribute to fitness – this, again, is perfectly true but as a bare fact it is also quite irrelevant. You can imagine a continent without any organic life but with a great deal of variation in the environment; and yet this has, again, nothing to do with fitness. It is the interaction between the genotypes and phenotypes on one hand and the heterogeneity, the changes of the environment, which is the important factor in natural selection. So to summarize once more, the two statements which you made are totally correct but largely irrelevant.

DR. EDEN: At this juncture, I really can't say anything. So far I see no difference between what you said and what I have said. You have explicitly introduced heterogeneity in the environment as well as heterogeneity in the phenotype. Clearly that is an empirical fact. I don't know whether it is worth trying to carry this discussion any further right now. I have to think about what you said and perhaps read what you have written. But, to repeat what I believe I said: There is a certain continuity in the properties of the organisms which exist; the continuity is carried from parent to child, and each successive generation is presented with an environment, including the inanimate world around it, the physical properties of that inanimate world and other organisms. As a consequence certain of them survive and certain of them don't. Those that survive will continue to produce according to their kind, with variation of course. So, I am still puzzled by your statement that we are saying different things.

The Chairman, DR. MEDAWAR: I was puzzled by your saying that these were vacuous statements. They are not vacuous statements. They are so, each one of these statements.

DR. EDEN: No, no, those two statements are by no means vacuous; but they are not a theory.

DR. C. H. WADDINGTON: I am a believer that some of the basic statements of neo-Darwinism are vacuous; and I think there is a confusion here, possibly, about whether we are talking about Darwinism or neo-Darwinism. Dr. Medawar mentioned this phrase, "the survival of the fittest," and it is a very elementary, old-fashioned, long outdated concept; but, of course, this is what Darwin was talking about. By "fittest," he meant best able to carry out the functions of life, best adapted to some environmental situation and some way of life. By a fit horse, he meant a horse that could gallop fastest and escape best from wolves, or whatever it might be. That is a real theory which is perfectly capable of refutation.

What has happened to it since, in the process of turning this into a lot of mathematics, is that "fitness" has been redefined, leaving out anything to do with way of

life, simply in terms of leaving offspring. So the theory of neo-Darwinism is a theory of the evolution of the changing of the population in respect to leaving offspring and not in respect to anything else. Nothing else is mentioned in the mathematical theory of neo-Darwinism. It is smuggled in and everybody has in the back of his mind that the animals that leave the largest number of offspring are going to be those best adapted also for eating peculiar vegetation, or something of this sort; but this is not explicit in the theory. All that is explicit in the theory is that they will leave more offspring.

There, you do come to what is, in effect, a vacuous statement: Natural selection is that some things leave more offspring than others; and you ask, which leave more offspring than others; and it is those that leave more offspring; and there is nothing more to it than that.

The whole real guts of evolution—which is, how do you come to have horses and tigers, and things—is outside the mathematical theory. So when people say that a thing is vacuous, I think they may be thinking of this part of it, this type of statement. The sheer mathematical statement is largely vacuous. The actual way this is applied, not by the mathematical theorists but by the biologists working with the subject, is not vacuous at all.

Dr. Alex Fraser: I think, if I get correctly what you were saying, that there is a genotype space which is of almost infinite size, and that you can imagine restrictions being put on this by the physical universe. I don't think anybody would find this as being a new statement or one that is not perfectly acceptable.

I think what was missed, though, in your genetical argument, is the fact that the genetical system in itself, and in its evolution, is a process of restricting that space; so that the ensuing sub-sample starts taking on much higher probability orders, once the evolutionary process has started.

An illustration, I think, can be given in terms not of nucleotides but of whole chromosomes. There is an evolutionary process in Drosophila involving the order within the chromosomes, namely, different inversions; and as one looks at this it seems a most improbable business in terms of differing inversions being established. J. T. Patterson, I think, made the calculation that in any species of Drosophila over a few hundred generations 500,000 separate inversion events will occur; in which case, what is improbable is not that you have established inversion polymorphism in its various forms, but why hasn't there been a much greater variety of inversion polymorphism established?

The selection system takes sub-samples through this genotypic space easily. I have students working in 2^{30} and 3^{30} genetic spaces on a computer; and they take this as quite a normal process. What is surprising, to me anyway, is how many times you get the same answer coming out when you deliberately specify to the computer that it should not be restricted in its answer, when you have kept your genetic scheme as wide and as unspecified as possible.

The Chairman, Dr. Medawar: Would you like to answer that, Dr. Eden?

Dr. Eden: I think I would have to know more of the details. I agree with you fully that the mechanisms which have been proposed, whether they are recombination mechanisms or mutational mechanisms, certainly constrain the space. What I would like to find is the characterization of these constraints. Clearly, we have the evidence available to us, namely, that we are alive, and the evidence that life has developed to this state in a relatively small number of generations; so we have what a mathematician might call an existence theorem. There is some path by which we have arrived at this relatively small corner in this large space, on the basis of a relatively small number of generations. What I am claiming is simply that without some constraint on the notion of random variation, in either the properties of the organism or the sequence of the DNA, there is no particular reason to expect that we could have gotten any kind of viable form other than nonsense. It is the character of the constraint that makes things possible, not the variation. That is the point I have been trying to make.

With regard to your experiments, I cannot comment without knowledge of your procedures. You are certainly right, you can work in spaces of 2^{30} or 3^{30}. We certainly cannot now, or, as far as I can tell, perhaps never, work with computers in spaces of 2^{300}. So in that sense we can't ever answer the question as to whether there are other domains in this tremendous space which are equally likely to be carriers of life.

What I am struck by is the fact that we seem to occupy a rather small corner of the space, as shown by the rather crude tests that I have been able to put on it, for example, the distribution of amino acids. What the characterization of constraints with regard to the distribution of amino acids is, I am not quite sure. Presumably, there are some that are purely physico-chemical. There usually are large numbers of glutamic and aspartic acids. Usually there are a large number of glycine and alanine residues, and so on. The range of charge variation in a protein is severely restricted, and presumably these are physico-chemical constraints. They should be looked for and taken into account and that is essentially what I am trying to say.

There may be other constraints as I have also tried to say. There may be constraints simply having to do with what I might call the syntax of the DNA chain. There is no question that the frequency with which mutation can occur is a function of the general organization of the gene or the chromosome in which a particular locus occurs. Again, I would presume that there are physical laws which control, but these laws need not necessarily be physical ones. There are biological mechanisms, biological repair mechanisms, biological error-correcting mechanisms, that have been identified and presumably they too act to constrain.

DR. V. F. WEISSKOPF: I am, of course, completely ignorant in this field but I thought we ought to discuss some of the special statements which struck me in Dr. Eden's talk rather than the philosophical statements about vacuousness. Discussions about the latter seem to me to be like medieval tournaments; you begin to offend your opponent before you really start fighting.

For example, there are two points which struck me and which I would like to have the experts explain. One was the business about the development of hemoglobin. It seemed to me to be the straightest way to come to the variations we find now. The straightest way is, of course, a very improbable one. Why did nature take it? The other point is the question of the groupings of genes. Is it not most puzzling that genes that are operationally similar are also located near each other in the DNA molecule?

DR. EDEN: Can I just repeat, both for the benefit of Dr. Weisskopf and the other people in the audience, what I said in both instances, at least as I reflect on my reading in this field. First of all, with regard to the DNA code, as you recall, the theory suggests that there are three consecutive letters in an alphabet of four types and that corresponding to every triplet of the possible 64 there is some amino acid. Suppose we were to change one of these letters in a sequence of three. Whether the currently defined code is correct or not is really immaterial. There are details that undoubtedly will be cleared up, but the code has been completely worked out. I can now make nine distinct substitutions, putting in any one of the other three letter types in any position. I can then ask, How many of the amino acids can arise from any particular triplet? It turns out, empirically, that almost all possible transformations lead to a different amino acid. The maximum number would be nine and, as a matter of fact, the average is about eight. It could be seven and my argument would not change very much; so that is the first point.

DR. WADDINGTON: Surely we can go along with this point.

DR. EDEN: The second point can be illustrated by the lac operon. It is simply saying this: If I intend to go from one protein type to another protein type through a long chain of single changes, as in the two subchains of hemoglobin, I can compute that it would require a minimum number of 120 changes.

DR. MICHAEL LERNER: I think that this is not right at all. I think most of the changes may be reading frame shifts. They are not substitutions; they are insertions or deletions.

DR. EDEN: The evidence seems to be against either insertion or deletion. I am sorry I don't have the illustrations here, but if you look at the two alpha and beta subchains within the hemoglobin, what you observe is that there are long stretches of sequence identity throughout the chain interrupted occasionally by a single amino acid difference. You have to open up the chain in certain places and leave room for one or two deletions or insertions; but there is a point-for-point agreement throughout the whole chain. Roughly speaking, one-half of the chain has not changed. This procedure may have gone by shifting, by misreading, by missing, etc.; but somehow all these insertions and deletions ended up with the two molecules looking very much alike when they are put in register. I find that implausible.

DR. LERNER: There is a very good reason for it; because for every deletion at one place you have to have an insertion somewhere else. Otherwise, you get only nonsense; so there is an automatic restriction.

DR. EDEN: Not necessarily.

DR. LERNER: Usually there is.

DR. EDEN: No, because in this particular case they happen to be of different lengths; so at least six times there must have been an addition or a deletion without getting nonsense.

DR. LERNER: But this is a whole triplet. I am talking about single nucleotides, not a triplet, just a single nucleotide insertion.

DR. EDEN: A single nucleotide insertion will change a single letter.

DR. LERNER: No, it changes the whole reading.

DR. EDEN: Yes, you are right; but I still don't see your argument.

DR. LERNER: You can't compute the number of mutational steps that have occurred on this basis because you don't know exactly what happens.

Question: If such phenomenon would have happened in a frequent manner, the change would be entirely different.

DR. FRASER: Not if there were a restriction in the hemoglobin, a constraint on some part of it but not much on the other part; in which case you would expect one bit of it to have the key function left, and natural selection is holding you to this; but reading changes can shift the other bit around.

How many mutation steps are involved in this at the present moment it is not possible to calculate. You can't make any statement of sets. If you are going to talk about nucleotides, then you should count the nucleotide changes. I think Lerner is quite correct—to make a statement from amino acid changes as to how many mutational steps there have been is not at the present moment possible.

DR. GEORGE WALD: I want to ask Fraser and Lerner why one doesn't find hemoglobin diseases in which this phenomenon you are talking about has occurred? Each hemoglobin mutation involves the replacement of one amino acid in the sequence by another, hence one nucleotide in the DNA sequence of the corresponding gene by another. I don't know of any instance in which one has yet discovered a hemoglobin with a long run of shifts.

DR. MAYR: Because it doesn't survive.

DR. WALD: All right, then it doesn't enter our argument.

DR. EDEN: On the other hand, we know of hemoglobin diseases in which it turns out that a perfectly adequate explanation is made simply by assuming that there was a single nucleotide chain in a single position in approximately half a dozen hemoglobin types. It turns out in this half dozen, or dozen by now, of hemoglobins, which differ in a very few positions, that each one of the transitions can be explained by a single DNA change.

DR. LERNER: I'm sorry, I still consider that irrelevant. You don't know how they arose; you only know that that is what they are. You know that there has been a substitution; but experimental evidence on mutations suggests that tautomerization is a very rare thing, that normally what you do have is insertion or deletion as a mechanism of mutation.

DR. EDEN: In that case, I think I would conclude from what you are saying that my estimate of the number of changes required is very, very minimal. There is no way in which it can be smaller than the 120 I suggest. To reach the same end product by a sequence of insertions and deletions would require a vastly larger number of steps, which makes it worse.

DR. LERNER: No, the other way around.

DR. WILLIAM BOSSERT: For example, one could imagine a double deletion and a single deletion some distance apart. In fact, then, with two acts or three acts, you have changed quite a range of the chain, quite a range of the amino acids. So, it is not one chain per amino acid, in fact, but two acts, one in each twenty.

DR. EDEN: That is right, but I come back to what I said before: If we look at the two chains, the alpha and beta chains, what we find is that there are long stretches in which they agree and other stretches in which they disagree. Suppose there were changes in several places at a time; we would expect some transposition one way or another. It is an empirical observation that we do not find it.

You may very well be right in that it may not be possible to compute the number of changes necessary to go from one form to the other. I do not claim to have done so; I am computing a lower limit only.

DR. J. L. CROSBY: There is one point which I think one has got to remember. All the intermediate changes—or am I being extra simple—have got to be viable. It seems to me that you may be able to say that if your changes take place by reading frame shifts, we would need fewer of them. But, your reading frame shift seems to decrease enormously the possibility of intermediate stages being viable. This isn't a set of models we have got on a bench or a set of pretty pictures on a blackboard. We are going through a series of stages, each of which has got to be capable of existing viably, if it is going to have any possibility of giving rise to the next. We must bear that in mind.

DR. SIDNEY FOX: We have been vexed by one of the main problems that has apparently concerned Dr. Eden, the fact that such a very minute number of contemporary proteins exist against the background of the theoretically possible number of isomers. We are also provoked by the relatively high proportion of glutamic acid and aspartic acid which he has referred to. Some years ago, as an outgrowth of both of these considerations, we found it possible, under conditions that can be imputed to the geological environment, to combine all of the amino acids of proteins simultaneously in single polymers which have many of the properties of the proteins. The first syntheses occurred when sufficient proportions of aspartic acid and glutamic acid were heated with other amino acids.

At this point, I should comment on Wright's statement, cited by Dr. Eden, that prebiology has no relevance to evolution. If we accept that statement, we are in the position of believing in a discontinuity between pre-life and life. While such an inference may be defensible for prebiology and selection, I believe it is not for prebiology and evolution, unless one equates evolution to selection.

The most astonishing consequence of these studies of heating amino acids under the appropriate conditions is that the polymers produced have a markedly limited heterogeneity. This has been shown in many ways and it is outlined in the second paragraph of my working document. I think we should place this in apposition to another point of view, which is not well known, the observation first reported by Gamow, Rich and Yčas (Adv. Biol. and Med. Phys. *4*:23, 1956) that contemporary proteins, as judged across the entire panel of phylogeny, are close to random. This conclusion has also been drawn by Williams (Williams, Clegg, and Mutch, J. Mol. Biol. *3*:533, 1961), by Šorm (Šorm and Keil, Adv. Protein Chem, *17*:167, 1962) and by Vegotsky and Fox (in Florkin's Treatise on Comparative Biochemistry, Academic Press, New York, IV 1962, p. 185).

On the premise of a logical evolutionary span from pre-life to life and from preprotein to protein, the total picture is one of an evolution from a highly ordered primordial state to a considerably less ordered

state, when looked at purely from the standpoint of the protein.

This progression is in keeping with the second law of thermodynamics and contrasts with what I find often to be a supposition (Oparin, A. I. "Origin of Life on the Earth," Academic Press, New York, 1957 p. 185) that primordial protein was wildly disordered. Many speak also of order in contemporary proteins, when what is often truly meant is a biological repeatability of sequence rather than thermodynamic order.

This realignment of concepts leads us to some interesting new concepts. For example, variation in residue sequences in protein, for the entire gamut of organisms, is a basis for evolution. The necessary variety could conceptually be aided, or fixed, through the coding mechanism by nucleic acids. One role of the nucleic acids, then, would be to contribute to evolutionary changes by aiding randomization of proteins (Pattee, H. H., Biophys. J., *1*:683, 1961).

Dr. A. W. Kozinski: I have only one comment: So far as I understood your presentation, you have considered three parameters: first, mutation rate; second, generation time; and third, frequency of recombination. The frequency of recombination is what I want to reconsider.

I believe you have underestimated the frequency of recombination by assuming it to be stochastic, i.e., the successful recombination for different markers resulting from random meeting of two individuals.

It is important to introduce to computations another type of recombinant resulting in the formation of clusters of recombinants. There are numerous examples—transduction is the most obvious. I believe also transduction could play a very important role at early stages of primitive life on earth. In this system (transduction), a single individual might be a donor of perhaps 300 units of genetic markers at once *within one* generation of the organism.

I think that by introducing this into your calculation, one will eliminate the apparent paradox.

Dr. Ezra Shahn: My understanding of enzyme activity is that there are active sites, destruction or alteration of which would impair enzyme efficacy, which may be held in position by nonactive regions in which amino acids may be changed at will. It is conceivable that the protein configurations which are altered in the alpha and beta strands are of this latter type. If this is the case, and if I interpret your X's and dashes correctly, there are strings of such changes. It is precisely these which could be introduced by an addition and a deletion of nucleic acids. That is, two simple changes in a nonactive region of an enzyme could produce a whole string of changes. This would not require that each triplet be independently changed; and this total change within the strand would be able to occur without any impairment of function.

Dr. Eden: May I comment on that last statement? Your hypothesis is certainly an acceptable one; except, again, the evidence does not seem to be the case in the alpha and the beta chains. I have looked at the distribution of chain lengths in which these differ. It turns out that most of the chain lengths in which they differ are one unit long although there are some that are two, three, five and so on. The distribution of chain length differences appears to be random. If I had any way to compute what that distribution should be on the basis of some plausible model I would try to do so. The fact of the matter is, that there are many cases in which there is simply a single amino acid that has been changed with the contiguous sequences (left and right) being unchanged, and the two molecules themselves are very much in register.

Dr. Wald: I think it is important to stick with this factual discussion a little longer; because we are likely to be spending a great deal of time with matters that don't have such clear facts associated with them. I want, then, to support what has just been said. We have, by now, a rather large material, involving hemoglobin mutations, none of which as yet exhibits this kind of phase shift that is being talked about. Phase shift is a possibility, but not yet found.

I want to add a further note which has a large bearing, I think, on Eden's discussion. Having been a little challenged by something that Simpson recently wrote, alleging that all changes in proteins are adaptive, I took a little trouble to find

whether a single amino acid change in a hemoglobin mutation is known that doesn't affect seriously the function of that hemoglobin. One is hard put to find such an instance. Do you understand what I am saying? One talks as though there were at least long runs of the amino acid sequence that one could toy with freely, that don't matter very much. One is hard put to find a single instance in which a change in one amino acid in sequence does not change markedly the properties. The restrictions are enormous.

A third point, please, which is factual. I don't understand the basic argument involving these hemoglobins, or the cytochromes which have been worked out even better; because, in fact, on a very crude basis one finds that as you go back in phylogeny the number of such amino acid changes tends to increase in a quite regular way. If you make a rough estimate (and it is as rough as can be), it looks as if something of the order of 10 million years is needed to establish a mutation. That is, each of these single amino acid changes appears relatively frequently in individuals as pathology; but to establish one such change as a regular characteristic in a species seems to take something of the order of 10 million years. However, we have got the 10 million years; so I don't quite see the problem being raised in this regard.

DR. CONWAY ZIRKLE: Mr. Chairman, I wish merely to indulge in a little improbability, one that is at least as great as that cited by Dr. Eden. If we can assume, I think quite reasonably, that our parents were heterozygous for about 10,000 loci, we can see how slight the chances are that any one of us would have been born instead of some nonexisting brother or sister. The number of our ancestors also increases exponentially per generation back to a point where everyone probably is descended from everyone but, of course, in a different degree.

Now, what is the probability of any one of us being here in this room after the human race has been on earth for about one million years? I am convinced that the chances against any one of us having been born is practically infinite; and this forces me to accept a solipsism and to assume that this room is empty, except for myself, of course, and that the only existence any of you have is in my imagination.

DR. MEDAWAR: That would be a good place at which to end. However, we will continue.

DR. NIELS BARRICELLI: I would like to point out that if a mutation produces an extensive shift of reading frame in one direction or another, it most likely would be a very harmful or lethal mutation; but it would also usually be a recessive mutation which might not appear in any living organism. Still this could be the first step for another mutation which reduces the piece which is changed by the preceding mutation to a very small segment of the protein molecule. The result of these two mutations does not have to be lethal or harmful. It is perfectly consistent with present information to assume that such sequences of two or more mutations are very likely, particularly when we consider the abundance of recessive lethals in many populations.

The Chairman, DR. MEDAWAR: No more comments. Professor Ulam must now really have a turn. You will have an opportunity later perhaps to comment.

How to Formulate Mathematically Problems of Rate of Evolution?

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Thank you very much. Actually what I am going to talk about will be in the nature of a continuation of the discussion so far. I was especially interested in the remarks made by Professor Weisskopf and in the fact that our discussion started right away on a philosophical or even perhaps combative note. When I was about 14 years old, I was very much interested in mathematics and wanted to become a mathematician, but I read a lot of other things, too. Conan Doyle's story, "The Lost World", was a fascinating book. The main character, Professor Challenger, was a natural scientist. Those who have read the book remember, perhaps, his terrific temper and the violent debates in which biologists engaged at that time and how Challenger's terrible temper made such scientific meetings exciting. Now, at the age of 18 I attended a mathematical meeting and was terribly disappointed that nothing of the sort occurred there. It was all too calm and quiet. Finally, after all these years I find myself at a meeting which corresponds much more to my idea at the age of 14 of what it should be like. It is all very wonderful.

I believe that most mathematicians and perhaps the lay people, in general, tend to be somewhat congenitally neo-Lamarckinists. Some ten or twelve years ago we had discussions with Professor Weisskopf on problems of the sort discussed here. We both wondered how it appeared extremely unlikely a priori that in the short span of one billion years, due to successive random mutations, all the wonderful things that we see now could have appeared—somewhat like Professor Eden's remarks made today. As I said, it seems to require many thousands, perhaps millions, of successive mutations to produce even the easiest complexities we see in life now. It appears, naïvely at least, that no matter how large the probability of a single mutation is, should it be even as great as one-half, you would get this probability raised to a millionth power, which is so very close to zero that the chances of such a chain seem to be practically nonexistent.

But, I believe that the comments of Professor Eden, in the first five minutes of his talk at least, refer to a random construction of such molecules and even those of us who are in the majority here, the non-mathematicians, realize that this is not the problem at all.

A mathematical treatment of evolution, if it is to be formulated at all, no matter how crudely, must include the mechanism of the advantages that single mutations bring about and the process of how these advantages, no matter how slight, serve to sieve out parts of the population, which then get additional advantages. It is the process of selection which might produce the more complicated organisms that exist today.

As for myself, I have done a bit of very schematic thinking on the mathematics of such a process and I want to make some remarks to you which certainly are not, as one of the speakers stressed before, correct in a realistic sense but might be relevant for the approach to some quasimathematical discussion at least. The philosophical and general methodological remarks made by various speakers so far can form a basis of what can be, sometime in the future, mathematized. What I am going to do will con-

sist, as it were, of picking out various items from the comments made so far and try to show how, perhaps in some remote future, mathematical schemata can be formulated. All this reminds me of a story about two persons who collaborated on writing musical comedies. One of them was writing the libretto, the other one the music. One day they got together and one asked the other: "Do you have any ideas about the music?"

"No, do you have any ideas about the libretto?"

"No."

"O.K., let's go on and write the play."

Perhaps this is the situation now in attempting to make something like mathematical treatments of biological problems. It seems to me, nevertheless, even if it is a little premature, there is still good exercise in talking about these things; perhaps in ten or twenty years something amusing, or even useful, may come out of it.

Before any such thing will be treated mathematically one must have numerical values of certain quantities or parameters, which to a mathematician are just parameters or only letters; but, if one wants to use it in any biological illustration, one must have given numerical values for these. In my talk I will give you a whole set of such parameters with values it is important to know. The trouble is that at present realistic definitions of these parameters, not to mention the numerical values, are completely unknown.

First of all, let us start with a total number of some extremely primitive organisms, perhaps some simple bacteria or pre-bacteria which existed at one time, formed by some random combinations through a chemical process. If one wants to make it easier for the Darwinian Theory, this number should be taken as large as possible. N, then, is a number of some very primitive individuals which existed, say, a billion years ago.

The other parameter, which is obviously of great importance, is total time. T, that life has existed so far. This is, let us say, one billion years. I should tell you right away that all these "parameters" of which I am going to talk, are uncertain by factors of hundreds, thousands or more. This last one is perhaps better estimable than the others.

One needs also a number, τ, the lifetime of a single individual. Again, for our purpose, it is "better" to make it as short as possible. We want to have as many generations as possible, since mutations coming between them, then, are transmitted. Assume that it is just one day, for example. Now comes the only number which is easily computable on the basis of the other numbers, that is the number of generations that have existed. This is simply T/τ.

Now come really difficult numbers to estimate—first of all, the frequency of mutations per lifetime of one individual. These mutations might be due to cosmic rays or chemical mutagens. Their frequency we can call a. We want, however, not the frequency of all mutations but the frequency of the *favorable* ones, whatever that means. This number, even in some sense as an average one per individual (and there are different individuals, of course), is very hard to estimate. It is certainly very small.

The Chairman, DR. MEDAWAR: I don't quite understand alpha.

DR. ULAM: Alpha is the probability that there will be a favorable mutation.

The Chairman, DR. MEDAWAR: In what?

DR. ULAM: In the genetic makeup of one individual during his lifetime.

The Chairman, DR. MEDAWAR: At any locus, in any cell?

DR. ULAM: In any locus, in any cell.

DR. MAYR: In any germ cell?

DR. ULAM: Of its genes.

DR. WALD: What is favorable?

DR. ULAM: This could form a subject of a special and long discussion. I will merely try to define what I mean by "favorable" for the purpose of one very crude and oversimplified mathematical scheme. I have to warn you, should it be necessary, not to put any credence whatsoever on the value of these parameters. In some future mathematical theory it will, however, be necessary to get numbers for such values. It seems to me that just to start the discussion, the final probabilities, even if we assume some values from the present guesses, will not come to be as fantastically small as in Professor

Eden's conclusions; but we will come to that later.

Let us now assume that α is a small number, say 10^{-10}. Certainly as you look at the frequency of the radiation impinging on a small object during a short lifetime, one obtains extremely small values.

Now we come to another, perhaps more difficult, number to guess or to estimate. Call it γ. This is supposed to express the differential advantage of one "favorable" mutation. As Professor Wald has asked, how do we express it mathematically? Suppose that an individual received, by chance, a small "improvement" in his genetic makeup. How does one translate the value of it for the branching process of the replicating chain of living descendants? One can do it in many different ways. One way, purely mathematical, is to say that an individual which possesses this one tiny "improvement" relative to the other living organisms has a slightly better chance to survive; or to formulate it more easily mathematically, it has a slightly higher number of offspring than the other. Please note that we speak of one small mutation. If one wants to produce some organ like an eye, together with the whole apparatus of the nervous system connecting it with what we might call a "brain", one seems to need an enormous number of such successive steps. Let me stress one very important caveat. This point of view of a great number of successive steps is not really absolutely necessary. One might think of another process, involving operation with more abstract changes or "rules" than the mere accumulation of single pieces of "hardware" in succession.

But, naïvely, if one knows nothing about the actual world or even about biology, one might say a single one of a million successive improvements which culminate in something like an eye, does not confer any noticeable advantage. It is really very infinitesimal. Obtaining one improvement, which gives, say, a slight photosensitivity, gives a minimally greater chance for the individual to reproduce itself. Let us say mathematically that, instead of having just one offspring, one will have $1+10^{-6}$, or something of this order, offspring.

DR. FRASER: Alpha and gamma are confounded statements.

DR. ULAM: No, α and γ are related mathematically but they have their separate and different definitions. This is so because α, as Professor Wald noted, is merely the *chance* of getting something; then having gotten it, what is the value of it? This value, I repeat again, consists in an increased, but only by a very small amount, chance of having more offspring.

DR. WEISSKOPF: You mean $1+10^{-6}$?

DR. ULAM: Yes, in the first problem which I will mention we have only mitosis. A single bacteria reproduces itself or several bacteria like itself. In the first problem there is no question of sex. That will be our problem No. 2. I should tell you now perhaps that we have tried to play games on a computer with such a system. Of course, we chose different and manageable values of our parameters to do that, to make it practical in the sense that calculations could be done in a reasonable time. This first problem, called "Adam", refers to unisexual reproduction. The second problem which we have studied, called "Eve", involved a mechanism of reproduction which is "better"—in the sense that the offspring can inherit some good characteristics of the parents independently from both of them and does not have to engage in the hopeless game of waiting for a mutation to come. The third problem, which we called "Lilith", will deal with something to which I think Professor Eiseley made references in his talk; namely, the mating between individuals will not be assumed to be completely random as in "Eve," but the phenotypes are able to recognize similar ones, to some extent, and they mate with each other, producing better chances of more "improvements" for the offspring.

DR. WADDINGTON: We still can't understand gamma.

DR. MAYR: Gamma is what we call fitness, à la Fisher and Wright.

DR. WADDINGTON: But how do you measure 10^{-6}?

The Chairman, DR. MEDAWAR: It has a million and one offspring instead of just a million.

DR. ULAM: γ in this scheme has the interpretation that an individual which has one extra improvement has $1+\gamma$ descendants instead of 1. We now need another parameter and its value. Somebody has to tell the poor mathematician *how many* successive improvements are necessary to produce something complicated, such as the visual system. This is a great number, no doubt, since random mutations due to, say, cosmic rays seem to be in the nature of changing the value of one bit in a code. In a random process this reproduces just one change, mostly nonsensical, but occasionally will have the effect of one rather small addition or change in the resulting apparatus. Even if one could write down a description, so complete that the computing machine would be able to utilize it for formulations on a physically existing machine for "construction" of such an object, the number of words in this description must be a very large one, perhaps a million. Certainly within several or many powers of 10 these are unknown. However, let us now try to make a simple, really trivial, calculation by orders of magnitude. This calculation is illustrating something that I think Professor Eden had in mind. Let us assume that we have 10^{11} individuals. Each lives one day and let us say that the chance of a favorable mutation or "improvement" is 10^{-10} per individual. This way, on the average, there will be, let us say, ten individuals in the population that have received it per generation. Now, how long does one have to wait before the bulk of the population will receive this "improvement"?

DR. MAYR: It depends on gamma.

DR. ULAM: Exactly. It depends on γ. γ is, of course, a small number and with a tiny advantage given by this one improvement, let us say γ is 10^{-6}, it will take about 10^6 generations before most of the population is endowed with this improvement.

DR. MAYR: This gamma you chose is really quite unreasonable. Fisher and Wright also took extremely low gammas when they started; but the recent work indicates that very often a mutant has a 30 percent advantage—in other words, up to 70 percent advantage. The average gamma, and particularly the ones that do get incorporated, are really very much greater than what you have there.

DR. ULAM: No doubt. On the other hand, a naïve mathematician like myself would reason as follows: If you are going to produce a complicated object, say an eye, by many successive changes, any one of these gives only a tiny little bit of advantage for survival, if indeed any at all.

DR. WALD: It is very good. You have exaggerated the difficulties, so your argument is going to be a minimum.

DR. ULAM: Oh, you will see that even so it doesn't come out so bad.

DR. WEISSKOPF: You haven't heard his argument yet.

DR. ULAM: In 10^6 generations, most of the population will have this advantage even with this small value of γ. In 10^7 generations, say, almost all individuals will have it. Now, remember that we want not just one improvement but, say, 10^6 in succession. So we need about, say, 10^{13} generations and not much more.

DR. MAYR: Couldn't they all go on simultaneously?

DR. ULAM: This is extremely unlikely.

DR. MAYR: No, no.

DR. ULAM: Look, there will be only ten individuals which received an improvement in one generation.

The Chairman, DR. MEDAWAR: In one locus?

DR. ULAM: I am speaking now of specific loci which determine the eye.

The Chairman, DR. MEDAWAR: Why?

DR. ULAM: I want to produce 10^6 improvements in succession.

DR. ZIRKLE: Between thirty and forty years ago a tremendous amount of work was done on mutation rates and on the mutation types. Don't you want to refer to those at all?

DR. ULAM: No. Of course it could mean that I am taking such naïve schemes too seriously.

DR. LERNER: I wonder whether that estimate of 10^7 checks with let us say, the facts that Dr. Kettlewell knows about.

PROFESSOR R. LEVINS: Why don't we challenge the model after we disagree with the results?

DR. ULAM: In contrast to the tone of the discussion I, personally, believe that the numbers I took are very optimistic rather than the opposite.

But, let me tell you that if it comes to schemes as simple as that, there is a very nice and simple mathematical technique for describing processes starting with a single object, which then duplicates and gives 0, 2 or 3 or more descendants. It is called the theory of branching processes. It deals with asexual reproduction and gives methods to calculate the number of existing particles, of various kinds, in future generations, and other questions of this sort. I would like to stress that a corresponding theory for branching with "sex", where particles get together, say, at random and then produce offspring, i.e., a combination of a binary process of mating and of reproduction, is mathematically much more difficult, and no exact theory exists as yet. The first theory is linear, to use the technical term—at least the expected values for the numbers of particles of various types, at various times, are obtained by repetition of a linear operator. This mathematicians know quite well how to handle. When we have two sexes and the process involves random pairings and reproduction, even the expected values of the fundamental quantities become quadratic functions. If one iterates such quadratic operators, the thing becomes very complicated and only the crudest beginning of a mathematical theory exists so far. If we have two types of particles, one has the following situation. First of all, we assume a random pairing. Then each pair, just to simplify it mathematically, produces exactly two offspring. We will allow some pairs to produce a little more than two, on the average, let us say, $2+\gamma$, where γ is a small number, i.e. a small fraction of the population will produce three instead of two. The value of the small fraction is determined by γ. Then the process repeats again and to illustrate it by a graph instead of a "tree", which gave a schematic picture of a nonsexual process by mitosis alone, we will have a combination of tree-like growth with loops which show which pairs mated. A continuation of such may be called, perhaps, a "pear tree".

It is amusing, just purely mathematically, to try to develop a little theory for this process. As I said before, it is much more difficult than to do it for simple trees. Coming back to the "biology" of it, one sees, and natural scientists have realized it for a very long time, of course, that the situation is more favorable. The offspring may inherit, independently, improvements from both parents. Suppose one parent has ten improvements and the other one has twelve improvements, perhaps different ones. Then there is a chance for the offspring to have as many as twenty-two improvements. This chance is quite small, if we assume that each improvement has a 50% chance of being inherited by the child. However, the chance of having, say, fourteen instead of eleven, which is the average, is not very small and, even though the expected value is just the average, even small fluctuations have a good chance to produce fourteen, as we said.

This is much more favorable than waiting for many generations for a random improvement coming through mutation. In this scheme then, the fluctuations, together with the survival of the fittest, leads to a much faster acquisition of "favorable" mutations than the pure mitosis problem. Please note that we cannot deal with it by calculating the expected values or means alone. It is the fluctuations, I repeat, and the mechanism of greater fertility of individuals with more favorable markers which lead to the acceleration of evolution.

I have forgotten to tell you, talking so far about the advantage which a single improvement confers, which we called γ, how to treat mathematically the advantage of having n more favorable markers than the average of the population. We treated it simply by using $n \times \gamma$ for the chances of more offspring. In other words, the relative advantage to an individual of having n more improvements than the average number in the population is a chance of $n \times \gamma$ of having an extra child. At first it seems that one cannot really use this recipe because if n is very large, the number of offspring would become nonsensically large compared

to the rest of the population. The point is, however, that in the actual processes calculated n never exceeds a very modest value, say, ten or so. To describe quite completely or rigorously the scheme that we have tried out on computers would take much more time than I have now. However, let me tell you that it is essential for following the population on a computer, or even in any mathematical treatment, to "normalize" the population in such a way that the total number of individuals never surpasses a fixed given value. A supercritical system will have the number of individuals tending to infinity. In reality the globe is a finite space and the total amount of food available is also finite, so in dealing mathematically with such an expanded scheme, one has to cut down periodically the total population to a fixed number of individuals. This is one of the reasons why an analytic formulation of the problem, using differential-integral equations, is very difficult and would be unrealistic. A numerical investigation is, therefore, not only the thing to do in practice but the problem really is a finite one.

To anticipate what I am going to tell you later, the result of calculation is that in a population with two sexes, the average number of improvements as a function of time or generation number increases rapidly—it is much better than the purely linear process of one sex. Let me stress it again—the great rapidity of the process of acquiring new favorable mutations in the problem of two sexes is due to fluctuations by which the offspring acquires more than the average of the two sets from the parents. The problem has to be considered in such a way that the population is periodically normalized to a fixed number due to the finite amount of food available. Secondly, the relative advantage of an individual with n improvements over the average in the population is a linear function of n. It is these two assumptions together that make an analytic formulation of the problem difficult, and the behavior for a finite population cannot be imitated by a mechanical scheme dealing with a potentially infinite population.

DR. SCHUTZENBERGER: Is the average always increased; or are you enhancing the chances that it converges?

DR. ULAM: Yes, always increased.

DR. SCHUTZENBERGER: How much faster?

DR. ULAM: The growth is quadratic or faster than quadratic, i.e., the number of improvements in the average of the population grows that rapidly, being a function of the number of generations, i.e., time.

DR. WADDINGTON: Can I ask how this differs from the standard biological theory that sexual reproduction speeds up evolution enormously?

DR. ULAM: Obviously common sense tells us immediately; the whole point of pursuing a mathematical model is to get some quantitative estimates and a feeling for the difference in the rate of growth.

DR. WADDINGTON: Yes, quite. This was the basis, of course, on which Sewall Wright, Fisher, and everybody else, worked on the problem of population with bisexual forms where you have very many possibly advantageous genes floating around in the population, so that you often have situations wherein things have 10 or a dozen advantageous possibilities.

DR. ULAM: Yes, of course, there are the very mathematical discussions of Sewall Wright employing rather complicated integral-differential equations, etc. However, it seems to me that this is terribly theoretical so far. One has to put actual numbers in it. In addition it seems to me that all these schemes neglect the role, to a large extent, of the fluctuation in obtaining the parental genes by the offspring. This alone, it seems to me, is responsible for the increase in the rate of growth.

DR. BARRICELLI: I was thinking that Fisher treated the subject of sexual reproduction in a very simple way and he expressed his results in what I would call Fisher's Law. This said that a species with sexual reproduction has a speed of evolution (measured either by number of mutations or by the improvement, meaning the number of mutations multiplied by the selective value of the mutation) proportional to the number of genes. A species without sexual reproduction is to be considered as a species with only one gene. In

other words, sexual reproduction represents an improvement by a factor of several thousand in the speed of evolution. The application of this law is, however, subject to the following basic restrictions. The genes must be in a position to act independently both phenotypically and genetically. They must be separable from each other by crossing over, and also each gene must control a phenotypic character without interference from other genes. If two genes interfere phenotypically or if there is not an adequate frequency of crossovers between them, they cannot always be counted as separate genes in the application of Fisher's Law.

DR. ULAM: All this is obvious, without any mathematics, as I said before. But the questions as to how much more rapidly the process will go on are really quantitative. By the way, our third problem, which we intend to run on the machines, will not deal with random mating between parents, but it will be set up so that individuals with a greater number of improvements will tend to mate preferentially among themselves, e.g. an individual with 25 improvements will be more likely to combine with another with 20 improvements rather than with some which have only four or five. This might again speed up the process of increase of the number of new and "better" genes. However, there is a caveat: Inbreeding, if pursued too long, will tend to nullify the ease of obtaining the new genes which come by mutations into the population.

Sometime, of course, one will have to try to put some realistic parameters in such models and here is a great problem. One has to interpret the nature of genes or the action of *some* genes in a somewhat more abstract way than has been done heretofore, either in general discussions or in models. Let me try to explain this. When Dr. Eiseley talked about the phenomena which have become of interest in physics during the last ten or twenty years, the so-called cooperative phenomena, he stressed the point that a group of *things* or a group of *rules* behaves differently from the mere sum total of the individual components. In our situation it means perhaps that the action of a collection of some genes is not merely a sum total of their individual actions but we get an action of what mathematicians might call variables of higher type. It is the *recipes* or *rules* of coded sentences which do more than the individual actions added together. There are probably genes whose nature it is to code or to program the actions of others. There may be even genes controlling, logically, still higher schemes; i.e., operating on classes of functions, etc. It is entirely possible that by some recursive rules the very prescriptions for action follow, reacting to the factors of the external world, producing from a small number of symbols or objects an ever growing variety and complexity of new prescriptions. Therefore, it is not clear at present how many bits of information are really needed to define even very complicated entities like ourselves. Perhaps this number is rather moderate or even small. I myself have written a note on such patterns of growth of figures. They are defined by a simple recursive rule, but in the process of growing assume later on unbelievably complicated shapes without intervention of new "mutations". Some people now, including myself and I believe Professor Waddington, are thinking about such possibilities. If this can be formalized or pursued on more "mechanistic" models, it might be that our whole discussion now on whether there was enough time for evolution and selection to work would be completely premature or irrelevant or wrong.

DR. SCHUTZENBERGER: Not vacuous.

DR. ULAM: No, not vacuous. I tend to believe, in fact, that indeed these first attempts of mathematical formulation of simplified models of evolution have some value. Of course, the game that nature plays is really much more complicated, even from the purely logical point of view. It seems to be a game between different branching processes, each going to infinity. The question is how to formulate, without going into teleology or metaphysics, these more functional or abstract properties of genes. No doubt such formulations will come. To a layman like myself, the discoveries in molecular biology of the last fifteen years, following from the discovery of the idea and the mechanism of the code, are extremely impressive. One still does not understand,

as far as I know, the program for translating the code into action: why and how the transfer RNA goes to different places, does what it is supposed to do, and how the course of *action* follows from the code, which prima facie seems to dictate only recipes for mechanical or chemical actions. All this must mean that some codes have more abstract interpretations than merely rules for chemical combinations. I am not saying that in every cell there exists an analogue of a brain which operates with instructions but undoubtedly the code must contain some elements which deal with rules for construction and *organization* and, therefore, are different from the, so to say, lowest level of recipes.

I would like to show you some of the actual results of computations. To those of you who are interested in arithmetical exercises of this sort, I might send copies of the graphs and listings of the rates of growth, etc., showing the speed-up of the process due to "sex."

Discussion

PAPER BY DR. ULAM

DR. WEISSKOPF: Dr. Ulam, you must know by how much this is going to be reproduced?

DR. ULAM: In our little problem so far, I think the number of generations necessary to produce a certain given number of "improvements" in problems involving sex was perhaps only a square root of the number for the corresponding unisexual problem.

DR. WEISSKOPF: You mean 10^4?

DR. ULAM: Not quite that small. I do not yet know precisely what we will get. As I say, the speed-up is intuitively obvious to everyone but to get it quantitatively, you must make many more computations and understand, which we do not yet, the properties of scaling down the values of parameters. When we change in a problem the value of a parameter like α or γ, the results do not change linearly, i.e. the slopes are not linear functions of the parameter. This one has to investigate much more, because it is only thus that one can get at more realistic questions. Some people here say that my numbers were pessimistic. If so, then in problems involving sex, the results would be surprising to me in the sense that not much more has been obtained by evolution than what we see in the world so far. Perhaps these numbers were optimistic.

Suppose you knew how to describe to the machine something like a human eye. One would probably need a little volume, say 1000 pages, for the description, detailed enough for some future machine to operate on. A thousand pages is half a million words. That means perhaps ten million bits.

DR. WADDINGTON: You could use algorithms. The whole business of trying to reckon on bits of information is inapplicable.

DR. ULAM: Exactly, as I said, there probably exist these other types of recipes, which are more general in the sense that they define rules by recursive relations, obtaining new things from the old ones more quickly than by blind or mechanical summations. Of course, these "abstract" genes themselves had to evolve from essentially nothing and it is this process which probably took a very long time.

DR. WADDINGTON: Could I put your question upside down? You are asking, is there enough time for evolution to produce such complicated things as the eye? Let me put it the other way around: Evolution has produced such complicated things as the eye; can we deduce from this anything about the system by which it has been produced? One possible deduction would be that the thing worked by algorithms rather than by describing bits. Actually, we know something about the ways in which genes do make embryos and how the organs are

put together. The genes do effectively act by means of instructions to carry out operations. But this means that in the whole of this sort of arithmetical question, you haven't begun to get numbers that have any meaning. I think you have got the question upside down.

DR. ULAM: It is possible to fall here into pure teleology. If the idea of the code itself was invented by random mutations, one has our whole problem anew again. We have to watch out, as Dr. Eiseley pointed out, not to fall into infinite regress.

The Chairman, DR. MEDAWAR: May I make a point here in support of what Waddington says? I think the way you have treated this is a curious inversion of what would normally be a scientific process of reasoning. It is, indeed, a fact that the eye has evolved; and, as Waddington says, the fact that it has done so shows that this formulation is, I think, a mistaken one.

I have been trying to put my finger on what it is that is wrong. I have the impression that mathematicians tend to think that what is selected in the process of natural selection is a mutant. That is to say, one starts with more or less undifferentiated mass of individuals, a mutation occurs, and then what is or is not selected is the mutant; but this is not so. What is chosen is a recombinant of some kind amidst a prodigious diversity of organisms. So arguments really based on the likelihood of occurrence of a given mutant, and the contingent probabilities associated with this, seem to me to be completely unrealistic.

DR. ULAM: Quite so; this was indeed my aim. It is a great challenge to mathematicians and logicians to produce schemata for formulating processes evolving by recursive rules and operating on such abstract entities as a set of prescriptions.

The Chairman, DR. MEDAWAR: But these do occur.

DR. ULAM: They do exist. There seems to be no question about it, but the problem is: how do they look and how do they work?

The Chairman, DR. MEDAWAR: I would like to apologize to you, Dr. Ulam, for singular ineptness in my chairmanship. I don't think you really had an opportunity to expound your views fully; but will people who wish to say something raise your hands now and let us have those seven in order.

DR. FRASER: On this point of fluctuation, I get the impression from listening to you that biologists have tackled none of these problems effectively and have looked at none of them. The problem of fluctuation and increasing the potential is at the present moment, I should say, possibly the biggest single means of publication in population genetics. These are coming out in a steady stream, and have been for some three or four decades. As for the problem of the maintenance of variability in cross-fertilizing organisms, the situation is the same—a vast stream of algebra, with a minuscule of biology.

I personally would like to say that there seems to be general agreement that when we get to cross-fertilizing organisms there is no problem. However, it does seem to me that in the absence of cross-fertilizing organisms one does enter into an area of reduced probability which is a real problem. But I rather seriously question whether there is such a thing as a completely non-sexual organism. The statement was made, "Oh, well, we are dealing with haploid single-line descent." Biologically, I think this is a rather fatuous idea; because even in organisms which are supposedly self-fertilizing, when people examine them and have a detailed look at them, they find that a minute amount of cross-fertilization occurs which is enough to maintain a huge pool.

DR. ULAM: Well, there is of course a phenomenon of transduction and so on.

DR. FRASER: A minute amount of crossing will hold a huge pool of variability. Consequently, your argument from non-crossing organisms is in actual fact a case which would possibly only hold in a laboratory under very, very restricted conditions. We are really concerned with the cross-combining type of organism where there doesn't seem to be any problem at all.

DR. MAYR: I must say I am really impressed by the tremendous agreement (and this is essentially what Alex Fraser just said) between what the more sophisticated mathematical analysis shows and what the biologists have believed in for the last thirty or forty years. I think the major correction

will have to apply to the relative sizes of these factors. For instance, we talk about 5,000 genes; actually, if you count the cistrons in a higher vertebrate, you come out with 5 million. We don't know whether these 5 million are all enzyme-making genes, or how many are regulator genes, or how many are antibody-producing genes, or goodness knows what; but right here you have a much greater figure.

What is the mutation rate in these? A cistron has, let's say, 1,000 nucleotide pairs. On the basis of what is known about the mutation rate of genes, let's take one mutation in 100,000. Then, with 5 million you come to the uncomfortable conclusion that every single individual in higher organisms has something like 50 mutations. Somehow or other this bothers us and we haven't got the answer for it. Perhaps the stated mutation rate is much too high. Another possibility which would shoot a lot of holes in this is the answer that only one out of 5,000 of these mutations is deleterious and will be noticed. Taking the cosmic ray-induced mutation as a sample is about the worst thing that can be done biologically, because it is probably the exception. The normal mutation produces something quite small, simply a shift from one code onto another that produces the same amino acid or some very minor change. Since it does not affect the visible phenotype it will not be noticed.

We know nothing here—I am talking from pure ignorance—but it is a challenging problem. It is quite likely that in many cases a mutation does nothing but establish another level of heterozygosity on another locus, another isoenzyme, or something like this; and it will be selected for because a certain amount of heterozygosity quite likely has a great deal of selective advantage. I am not talking about polymorphism or any of the spectacular ones. This afternoon I will talk very indirectly about this and demonstrate some evidence that seems to indicate this.

So, actually, the chance of having a favorable mutation is possibly higher by an order of maybe 10^5 than we know of right now. At least, it produces something that can be stored to be used when it may be needed. Gene pools have a tremendous storage capacity.

What about the gamma? I have already talked about that in the earlier discussion and I don't want to say anything more. I think gamma is much greater.

On the other hand, the kappa is a difficult thing because, as Waddington and Medawar just said a gene produces, let's say, an enzyme. All right, suppose we have 1,000 different kinds of cells in a higher organism—brain cells, nerve cells, skin cells, gland cells, and whatnot. All of them carry the same gene locus; potentially, the enzyme could be produced in each one of them. It depends on the postulated (and surely they must be there) regulator genes, when each is turned on and in what amount. Kappa somehow or other has to incorporate this. If a given gene is selected for because it does something good in the eye, what does this same gene do in all the other cells of the organism? That is a thing we have never taken into consideration and the evolutionist is very simple-minded about this. He takes the total average and says, "Well, as long as the phenotype as a whole, in terms of selection, is improved we have got something there." So all I am saying is we have so much variation in all of these things that somehow or other by adjusting these figures we will come out all right. We are comforted by knowing that evolution has occurred.

DR. ULAM: My aim was not, of course, to present to you something very revolutionary or very new but rather to show in an elementary way how one should ask questions involving quantitative problems, or how more logically and mathematically precise models could be made to work. May I ask the biologists the following: Do you believe that it will be possible, within the next five or ten years, to define more meaningfully the parameters which I called γ, k, etc.—there will be many of these, depending on the situation. There will be not just one k or γ, depending on the particular organ or the particular direction in which one wants to go. Do you think that one will be able even to give some numerical values to some of these?

DR. ZIRKLE: I would guess some of that had been done about thirty years ago.

DR. ULAM: This is hard to believe because I see, with all your reassurance, considerable diversity of opinion right here among biologists present at our meeting.

DR. LEVINS: I think that there is an error of strategy in this approach, in attempting to build up a system from its components. Somehow I feel that molecular events are more fundamental to evolution than population events. I believe almost no discovery which can be made about the code at the present time will be relevant to evolutionary theory, beyond the fact that variation does occur. We know that there is so much variation in populations that even if you start with the same founding population and select for the same characters, they will usually be built up in different ways.

We know that the rate of evolution has varied a great deal in evolutionary time and this seems to be related more to fluctuating environmental conditions and to a kind of evolutionary drag between different parts of a system than to limits of available variation.

Therefore, I think the mathematical problem is for us to formulate entities on a populational and organismic level, rather than to attempt to construct them from these elementary processes that are only loosely coupled. For example, there is the experimental phenomenon of the "selective give". You can select a population for about thirty or forty generations for increasing wing lengths or some other similar character; and then the system begins to resist. There is a plateau which reflects, not the absence of genetic variability, but the fact that countless selective pressures are operative. If the population is allowed to stay there for some time, readjustments take place and a new cycle of selection becomes possible. Therefore, we have to define this notion of elasticity in the developmental system.

Similarly, we know that the rate of response to selection is modifiable by linkage, by interaction between loci, and such things; but knowing this can be developed, we can then treat the system as a whole, as a system which is attracting a variable environment in the face of uncertainty. We can consider the characteristics of this system without worrying too much about how the genetic variants are distributed over loci.

DR. ULAM: I would like to say that this would be, so to say, the next problem mathematically. One has several chains of organisms developing in such a way, but then there are competitions, struggles, and fights between these chains. This is a problem of still higher order when you have such systems interacting with each other. Does not this go a bit beyond the subject of our Symposium, which, I think, is devoted to the Darwinian or neoclassical problems of evolution?

DR. CROSBY: It always seems to me that there is such an air of gorgeous unreality when mathematicians come to deal with biological subjects and I think that is the case here. I cannot really conceive of the idea that the eye began to evolve in pre-viruses or pre-bacteria. When you start taking the first of your (I have forgotten how many) 10^6 improvements, you cannot really start with year X_0; it has to be 10^N, where N is 3, 4 or 5. That seems to me to place the whole of that calculation completely out of court.

I feel that mathematicians often take ideas of biology to amuse themselves, rather than to advance biological knowledge. They are quite welcome to take our ideas, which must present them with an enormous field of possibilities for mathematical maneuvering; but I do really think that if they want us to take these things seriously, they have to present them in a way in which not only do we understand them but in which they make biological sense. I think they have got to begin by making the thing as biologically sensible as possible. It is not biologically sensible to suggest that the pre-bacteria started evolving my eyes.

DR. ULAM: I did not say that at all. As you say, it is true that mathematicians create an air of unreality, which is very complex; and the biologist, on the other hand, may take an unimaginative point of view, being a little afraid of generalization or schema-

tizations. I did not say that the pre-bacteria was going on to develop an eye.

DR. CROSBY: You began there in this whole chain of events.

DR. JOHN C. FENTRESS: Much of what I was going to say has been alluded to by previous speakers; but I think it might be interesting to take an analogy from recent work in neurophysiological mechanisms of information storage and integration. The reason for this is simply that there was a similar fad which people, borrowing from the work of mathematicians, jumped upon, i.e., defining information units in the nervous system. Some even tried to extrapolate and give quantitative estimates as to how much neural information a horse has and how much neural information a pig has, etc. The difficulty with this (and I think we are going to have an identical difficulty here) is simply how to quantify the amount of information you have, particularly when several different levels of analysis are being employed. You have to specify, first of all, all of your units which are invclved. Secondly, you have to be able to define the functional relationships between these units. Your estimate of information varies completely, as a function of the breakdowns and resynthesis involved in these steps. This, of course, relates back to the business of bits versus chunks which has been alluded to.

What the neurophysiologists are doing is turning in two different directions simultaneously. They are turning to Professor Waddington's type of qualitative mathematical approach where they can say something is a lot or something is a little, and this carries them very far indeed; or they are doing precise experiments on simplified systems in which they can actually define a few potential information units, and this takes them away from the original problem.

Just to give you one specific example of the types of problems you can get involved in, take your so-called favorable mutation. To estimate the rate at which this mutation occurs, you are apparently relating it back to a steady state. In other words, you have one favorable mutation within the organism; and, of course, it is mathematically possible, perhaps probable, that in conjunction with this one favorable mutation there are other mutations which are to the disadvantage of the organism. Therefore, these mutations in turn will greatly alter the chance of favorable mutations getting established, and so forth.

If the mathematician could state, given a final end product, that this is the *least* amount of information that he thinks is needed to achieve this final end product, it might be helpful. In other words, don't worry about how complex it *can* be; but simply state: "I can give all the instructions for an eye, with the most efficient programming possible, with *this* type of information coding." I think in most cases, the estimated minimum amount of essential information is greatly reduced when appropriate hierarchical and sequential programming is employed, and I think some of the problems raised by the first two speakers then disappear.

DR. ROY J. BRITTEN: I should like to make one comment about the difference in approach here which might perhaps clarify. You see, the "mathematician" is trying to proceed, from the beginning, by molecular mechanisms. In other words, he is using essentially a physicist's approach and this is obviously a possible route. The biologist thinks that in some way this has already been done because he understands evolution. I don't deny that he does understand the phenomenology of evolution. His understanding is not based on the satisfactory mechanism that the mathematician is attempting to reach for. It is essentially a new approach when you start at the fundamental level of molecular mechanism.

DR. WEISSKOPF: I am neither a mathematician nor a biologist and I would like to defend the mathematical approach a little. I think it is a way of model-making—which we know in physics—and models are very useful. I usually try to illustrate this by an anecdote concerning the Austrian timetable.

A Prussian once rode an Austrian train and it was, as usual, three hours late. He said, "Why do you have timetables in this country?"

The conductor answered, "If we had no timetable, we wouldn't know how late the train is."

There is a moral in this. We have to have first a basis on which we may know where to start and what we are talking about. It does not matter if this basis is a gross oversimplification.

All the arguments which I have heard from the biologists, as much as I understand them, are extremely important; but somehow I personally think that one must start with the simplest absolutely basic assumptions before we know whether this assumption is wrong or not. For example, to my mind it perhaps is not so interesting to take the "Adam" case of Ulam because, as I have learned here (and of course I knew it before), it has absolutely nothing to do with nature. But the next one is already a little nearer. To my mind, it is important to know whether such an absolutely simple conception is plausible or implausible, even if it is not a very realistic approach. It gives a time scale that, at least, is reasonable. This, to my mind, is an Austrian timetable which has some use as a starting point.

It seems to me we might adopt this methodology of using extremely simplified models. The biologists don't like that very much and perhaps they are right; but sometimes models are useful. That is the first general remark that I wanted to make.

The second is on the other side. I learned that genes are, if anything, extremely interconnected. That means a gene doesn't do only one thing; it does one hundred other things at the same time. Therefore, I don't really understand the definition of this gamma. For example, one gene might be an improvement that is extremely useful; but at the same time it changes a lot of other chemical reactions which are either neutral or not useful. But when they are not useful in one connection they are useful in another connection. I know you will tell me this is a simplified model, but I am troubled.

DR. ULAM: I have used the word "gene". In reality the gene as understood by the biologist is already a whole structure of things and probably there are many directives in it for many different things. A change in one position is probably specific macroscopically; but the same gene may influence many different phenotypic characteristics and, vice versa, many different positions and different genes may influence the same phenotypic characteristics. I really do not know.

DR. LERNER: I think the point is that gamma can be fluctuating. A gene which is advantageous in one environment or in one genotype may be disadvantageous in another one; but for each gene at any given moment you could compute the average value. I think that a lot of the simplified models have already been done by biologists, by Fisher, by Haldane, by Wright, who is still alive as is Muller. There is a tremendous literature on the subject using simplifications, but at least some of them may be more biologically sophisticated simplifications than the mathematician starts with.

The Chairman, DR. MEDAWAR: We must draw this discussion to an end, but Professor Mayr has a gloss on Austrian timetables.

DR. MAYR: I was once in the railroad station at Vienna in the 1920's, on the way to Graz, when I overheard a lady in a heated argument with the stationmaster, complaining that the train that she had been trying to reach had left too early. He said, "But, my dear lady, the train was 50 minutes late."

"Oh, yes, I know," she said, "but never before was it less than an hour late."

Mathematical Optimization: Are There Abstract Limits on Natural Selection?

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This will be a change of pace from the previous papers. My presentation will be on a much less general level. It does follow, however, a suggestion of Dr. Eden's that we might experiment with evolutionary operators such as mutation and natural selection on a level somewhat between that of the biochemist and the natural historian.

These operators have been examined to a degree in connection with the problem of finding maxima of mathematical functions defined on a number of variables, in particular the optimization problems of operations research. At first glance the process of evolution seems quite appropriate for solution of this abstract problem. Points in the space of variables can be removed by selection inversely according to the value of the function to be optimized at the point, the analogue of natural selection. New points can be generated by chance displacements from existing points, the analogue of asexual reproduction and mutation. Several applications of "evolution" optimization have actually been carried out using just these basic operators.

There are strong arguments against the practical use of the technique, however. In general it is less efficient, in terms of number of calculations, than alternative analytic methods. This is no surprise to the biologist. The rate of evolution in asexual organisms is relatively slow. Another difficulty is of more interest to us here. The evolutionary process, at least in the simplest abstract analogue, is akin to the general class of steepest ascent optimization procedures. Although such procedures in theory assure eventual convergence to the optimum, in the case of unimodal functions, in practical application on such functions, they often terminate in an *apparent* convergence to a non-optimum point.

We can examine some experiments which demonstrate this stagnation. Bremermann and Saloff (Experiments with Patterns of Evolution, Tech. Report, Univ. of Calif., 1963) at Berkeley applied the operators, mutation and selection, to the problem of solving a set of simultaneous linear equations, a problem which yields a unimodal fitness function. Each unknown of the equations was associated with a character under genetic control, assuming the operation of the genes was independent. Mutation rates for displacements in the two characters were set according to various underlying genetic models of control. The process of solution was then iterated—asexual reproduction, mutation, and selection—according to the fitness function, from an arbitrary initial point or genotype in the space of the two characters. Sometimes, rarely, the process led to the movement of the point or population of points to the position in the character space known to be the solution of the system of equations, hence the optimum genotype.

More often the result of the process was similar to that shown in figure 1. This particular case is not from Bremermann and Saloff but is something I have computed using the process mentioned. In this figure the two characters (unknowns) x_1 and x_2 can take on values linearly arrayed over their respective axes. The optimum genotype in this particular problem is for $x_1=4$, $x_2=5$. A typical evolutionary trajectory for a point, the surviving offspring in successive generations, is shown in the

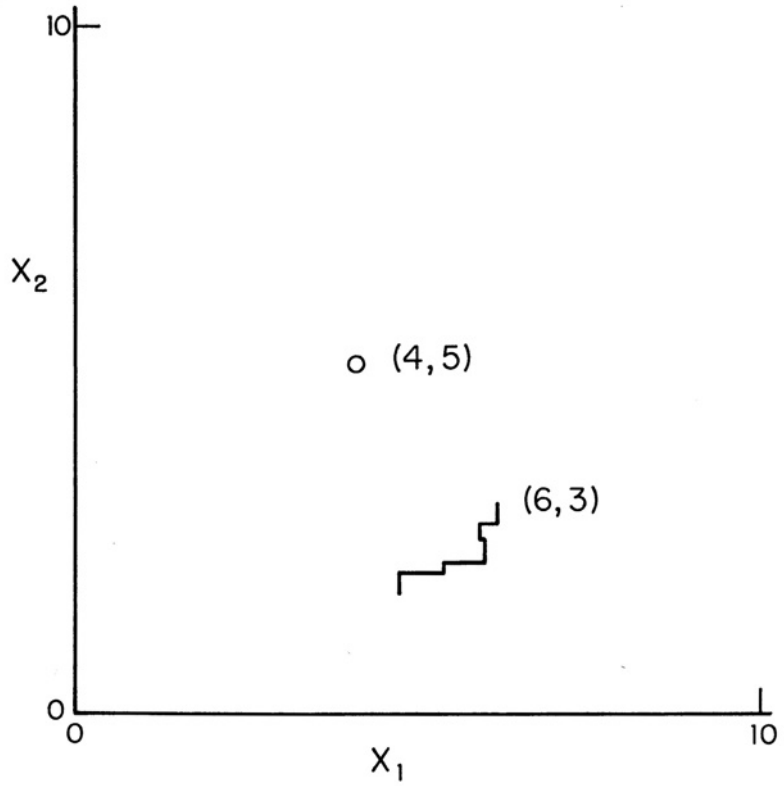

Fig. 1. Typical path of mean genotype, with respect to two characters, of a population evolving asexually under the fitness surface shown in figure 2. The population stagnates at $x_1=6$, $x_2=3$ instead of approaching the optimum $x_1=4$, $x_2=5$.

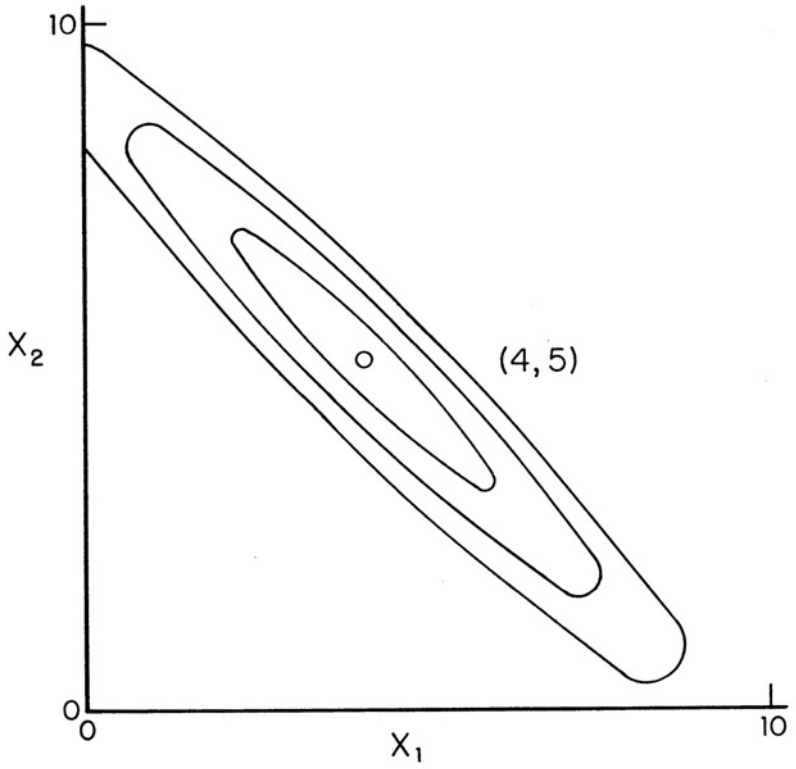

Fig. 2 The isoclines of the fitness surface discussed in the text, with the optimum at $x_1=4$, $x_2=5$.

figure beginning at about $x_1=4.5$ and $x_2=2$ and terminating not at the optimum but at $x_1=6$, $x_2=3$. The time course of this evolution was such that the movement from the initial to final point required on the order of 10 iterations of the mutation-selection process, while there was no further movement toward the optimum in 1000 succeeding iterations. The process had evolved a non-optimum genotype and stagnated. On examining the fitness function over which the process was operating, figure 2, we can come up with a ready explanation for this behavior. In this figure isoclines of fitness are shown about the optimum point. The actual values of the fitnesses are not of particular concern since selection operated in the process by removing less fit points, or genotypes, relative to others in the population. Picture this fitness surface in three dimensions. It is a long, thin ridge oriented along the long axes of the ellipses of iso-fitness. The point in figure 1 moved up the surface to a position directly on the edge of the ridge. From this position further improvement required a simultaneous change in x_1 and x_2, a simultaneous mutation at the two loci, in the negative direction for x_1, and the positive direction for x_2, of similar magnitudes. Whatever the underlying genetic model, such a joint mutation should occur with very low frequency, hence the stagnation. This simple model of evolution just does not contain any mechanism for the storage of genetic variability. Each mutation must occur at exactly the right time or be lost through selection. This explanation, as we shall see, is only partly correct.

A step which overcomes this particular difficulty is the inclusion of sexual reproduction in the process. Bremermann and Saloff attempted this and found that the difficulties of stagnation were not "automatically overcome." I found this to be true in calculations similar to theirs. The operation of mating and reproduction was defined explicitly as the production of offspring whose genotype was the arithmetic mean, with respect to all characters, of two randomly selected individuals in the parent population. Selection, again, was the removal of the least fit individuals from the population according to the function to be optimized, and mutation, the random modification of individual characters. The results of these trials in which the initial population was distributed uniformly over $0< x_1, x_2<10$, are summarized in figure 3. Here R^2, a holdover of the terminology of Bremermann and Saloff, is inversely related to the square of the fitness. Notice that on the average there was a rapid increase in fitness (approach to the solution) in the first few generations with much less change over the succeeding 1000 generations. I think it is fair to say that there is virtual stagnation here. Since, with mating, simultaneous movement in all characters is common, it is clear that our first explanation of the stagnation must be extended somewhat.

Consider the appearance of the fitness surface, figure 2, from a position on the edge of the ridge, that is, at the end of one of the long axes of an ellipse of iso-fitness. In any given circle on the character plane about this position, only a small fraction of the area is associated with an increased fitness. In the evolutionary process as defined in this simple model, even with mating, the population samples the fitness surface within some circle of variation and discards those individuals lying downhill in favor of those in the region of increase. The frequency of more favorable individuals generated will be small compared to less favorable individuals generated, when the population is on the ridge; hence the increase in population fitness must be small. By this explanation, which seems to be complete, the observed stagnation is due simply to the fact that on the edge of the ridge only a narrow angle of directions (assuming finite step sizes) leads up the ridge, as opposed to the flank of the ridge on which nearly half of the possible directions leads upward. This particular phenomenon could be of some biological interest since it contains within it the "curse of dimensionality"—the more characters involved, the stronger the effect. For example, if the ratio of favorable to unfavorable regions is $1/4$ in two dimensions, it would be $1/8$ for a comparably ridged function over three dimensions and less than .001 in ten dimensions. Fitness in natural populations is probably

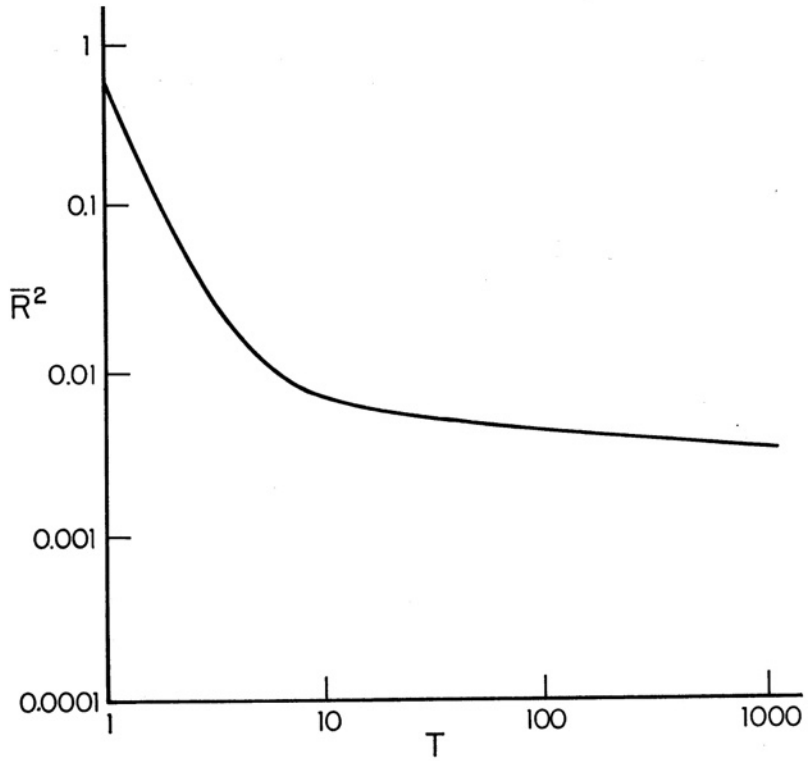

Fig. 3 Relation of average fitness to time for populations evolving sexually under the fitness surface of figure B-2. Time is in generations and $\bar{R}^2$ is inversely related to fitness. The curve is the average of nine populations.

dependent on a large number of characters, and stagnation could therefore perhaps be common in natural evolution. Beneath the conclusion, of course, is the assumption that mating, selection, and mutation in a population independent from all others, in a fixed environment, is a complete statement of the evolutionary process. Surely this could be accepted only in the rarest of situations. The phenomenon was interesting enough, however, to stimulate the consideration of additional operations in the evolutionary process in this particular abstract context.

A crude examination of the populations in the previous case seemed to indicate that lack of genetic variability went hand in hand with stagnation. The population, due to the possibility of rapid movement to the ridge but difficult movement thereafter, was usually compressed into a small region along the ridge with a low effective variability. There seemed to be two general, and recognized, evolutionary operators either of which might overcome this reduction in variability along the ridge. One would be to apply selection at a higher level, that of the population, as well as at the individual level. Explicitly this could be accomplished by introducing a number of populations, instead of one, into a single environment uniformly over the character space, letting them evolve independently as before, except that at random intervals the population with the least average fitness at the time is removed. In this form the process would merely select that population whose initial position in the space led to the most favorable position on the ridge, giving the stagnation previously found, although at a somewhat greater fitness level on the average. Only by the arbitrary insertion of populations after the beginning of the experiment or the addition of evolutionary interpopulation interactions to the process can stagnation be overcome. Both of these modifications are of biological interest; they will be discussed briefly later.

An alternative to selection by population in maintaining variability along the ridge

is, of course, varying the ridge itself; that is, through the introduction of heterogeneity in the fitness surface either with time or over locations connected by migration. The former provides an interesting problem in automatic control and, by the way, evolutionary theory. Clearly, very small translations of the fitness surface over the character space possibly, with time, will not significantly displace the population from the ridge to provide any valuable increase in the frequency of more favorable genotypes. On the other hand, too large or too rapid a translation might keep the population always far from the ridge. There is then some range of translation rates at which the population can track the ridge, so to speak, but still not be caught on it. The relationships surrounding this situation are probably well-known for a deterministic ascent procedure and perhaps could be obtained for our evolutionary process. It was the introduction of heterogeneity over locations that I considered here. A number of environments with different fitness functions over the two-character space of genotypes was defined. The optimum points, orientation of the axes of the iso-fitness ellipses, and the eccentricity, or "ridgedness," of the surface were all selected at random for each environment. A number of populations equal to the number of environments was selected and placed in each. At random intervals migration was permitted by the transfer of individuals between environments, introducing them into the instance of their population in the new environment. A modification involving the selection of populations and speciation as well as migration produced results quite similar to the simplest migration system. In this case the original populations were placed in each of the environments as before. At random intervals the least fit population was removed from a randomly selected environment and replaced by a copy of a second population selected at random over all populations and environments. This introduced population recognized no kinship to other populations in the environment and began an independent evolution. The results of a number of trials of this type are summarized in figure 4. A comparison of this with figure 3 demonstrates that the stagnation has been overcome.

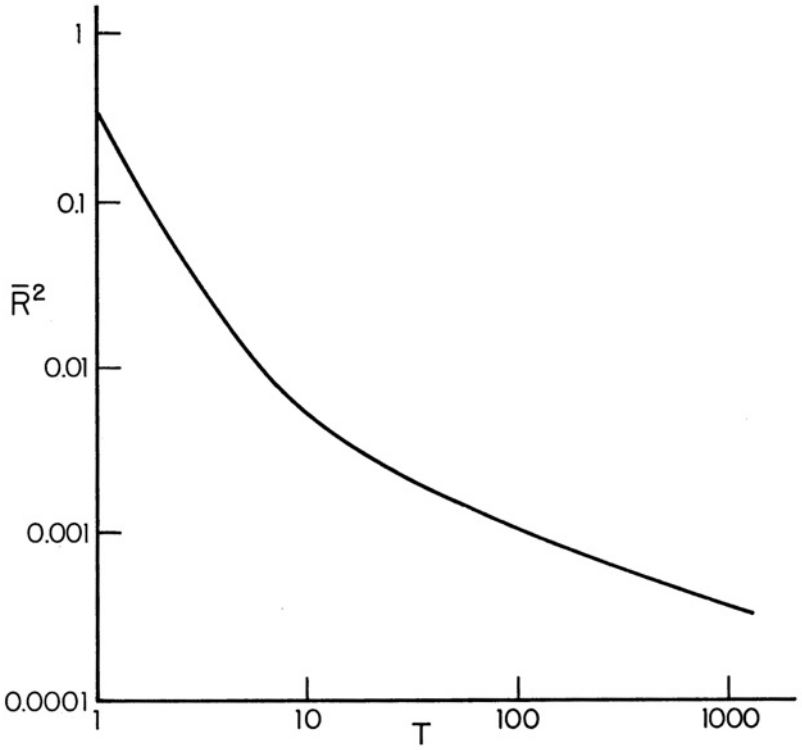

Fig. 4. Relation of average fitness to time for populations evolving under heterogeneous fitness surfaces with migration.

DR. WADDINGTON: What is the relative magnitude of the standard deviation in terms of your distance from the optimum?

DR. BOSSERT: The range in the populations was on the order of three-quarters of a unit by the scale of figures 1 and 2, although it was somewhat lower, I can't say exactly how much, for populations on the ridge of the fitness function.

DR. WADDINGTON: The variation is about 0.75 and you come to 0.001 away from the optimum in your earlier figure?

DR. BOSSERT: I must apologize for having been so vague on the nature of R^2 which appears in the figures. To explain it in detail requires a more complete definition of the abstract problem which led to the fitness function used. I had avoided doing this because it was of no biological interest except that it generated unimodal fitness functions over a character space such as the one shown in figure 2. I agree with you now, that it is important to complete the discussion of this point.

Recall that the abstract problem set was the solution of a set of simultaneous linear equations, e.g., in two dimensions,

$$a_1 X_1 + a_2 X_2 = Y_1$$
$$a_1 X_1 + b_2 X_2 = Y_2$$

where a_1, a_2, b_1, b_2, Y_1, and Y_2 are all given. X_1 and X_2 are to be determined. An arbitrary pair of values x_1 and x_2, corresponding to a genotype in our model, yields values y_1 and y_2 when substituted into the set of equations. The fitness of the trial values of x is not measured by their approximation to the solution but by the difference between the given values of Y and the y values they produce. Precisely,

$$R^2 = (Y_1 - y_1)^2 + (Y_2 - y_2)^2$$

This relation mapped on the x_1, x_2 plane gives the unimodal surface, with elliptic isoclines whose eccentricity is determined by the condition number of the matrix of coefficients in the system of equations. The R^2 measures distance in the Y plane, while population variation is interesting relative to distances in the X plane. The two are not directly comparable.

DR. ULAM: Isn't it true that there is no absolute standard of excellence or fitness; it is only a relative question, always?

DR. BOSSERT: Yes, and it was this thought that led me to neglect a definition of R^2 earlier. Between two individuals only the sign and not the magnitude of the fitness is of importance when selection is carried out in the deterministic manner as in the models discussed. Fitness can be tied, of course, to the probability of survival in which case the absolute magnitude is certainly of importance. One general criticism of these models and, in fact, of current evolution theory is that the concept of fitness needs to be broadened.

To summarize briefly, the basic evolutionary operators of mutation and natural selection do not perform well, in the sense of translating a population to which they are applied over a space of genotypes to that genotype which is optimum. The various groups of applied mathematicians who recognized this quickly discarded the operators as abstract mathematical tools and gave passing concern about the state of our understanding of evolution. The finding is no surprise and of little interest to biologists since mutation and selection do not complete the "neo-Darwinistic interpretation of evolution." Additional operators such as migration and selection of populations easily overcome the difficulty of stagnation at non-optimum fitness levels, which turned these particular mathematicians away. It is unfortunate that communication ended on both sides at such an elementary level. From the brief exploratory continuation I have made I feel that there are developments possible in this context which could be important in both disciplines.

Discussion

PAPER BY DR. WILLIAM BOSSERT

The Chairman, DR. MEDAWAR: Thank you. Exactly what do you mean by a broader view of fitness? In what way is it broader than the one we are working with?

DR. BOSSERT: I was disturbed, in our morning's discussion, that no one brought up the fact that fitness might be closely related to the adaptive form already achieved.

The Chairman, DR. MEDAWAR: How could it be otherwise?

DR. FRASER: Would you put that algebraically? Are you saying that the fitness is a dependent as a frequency-dependent function?

DR. BOSSERT: The fact is that the fitness is not determined solely by the environment; it is not a competition between individuals and the environment, but it is a competition of one against the other in the structure of the community of population so far defined. I hope we are going to get into this.

DR. LEVINS: Population mass curves your fitness space.

DR. BOSSERT: Yes, that puts it very concisely. This is the consideration I would hope to add to the discussion of fitness. Let's follow the displacement for several populations in a two-component space. In figure 5a two populations are introduced to the environment. The letters A and B stand for mean phenotypes of populations A and B. The deviations are not shown, but the variation in each population is on the order of one-tenth of the maximum range in each X and Y.

After a few generations, the populations displace as shown in figure 5b. A third population, C, has been introduced at this time. As we follow the displacement of these populations, we see they approach a configuration in the spaces which is quite independent of the order and exact values of the mean phenotypes in which populations are introduced into the environment.

Figure 5c shows the triangular pattern one would achieve in a couple of hundred of these selective steps, no matter in what

Figure 5 (a)

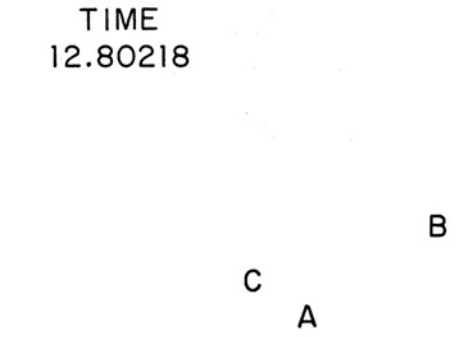

Figure 5 (b)

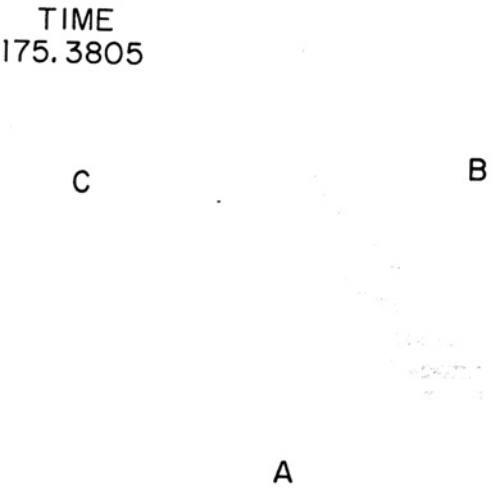

Figure 5 (c)

Fig. 5 Mean phenotypes of three populations with respect to two components of mating behavior. The standard deviation about these means is approximately one-tenth the total range shown in each case.

The time is given in generations:
(a) Initial contact of two populations; (b) Insertion of third population; (c) Pattern achieved after a period of displacement.

order the population had been introduced, and no matter what initial values of the components were used for each of the introduced populations.

DR. WADDINGTON: Under what auspices do they come into this pattern? Is this with exclusion of intermating or is this productivity?

DR. BOSSERT: This is due to the exclusion of intermating. There is no difference in fitness correlated with the two components assumed. Here the fitness function over this space has been warped by the populations themselves from a constant plane to a figure with three hills.

DR. ULAM: I do not quite understand some of your diagrams. Are you trying to say that there is no absolute function, i.e., a given function which measures what we call fitness but which really depends on the relative numbers; that is to say, the fitness of one individual is a function of the fitness of his competitors?

DR. BOSSERT: Yes.

DR. ULAM: Well, the game that nature seems to be playing is difficult to formulate. When different species compete, one knows how to define a loss: when one species dies out altogether, it loses, obviously. The defining win, however, is much more difficult because many coexist and will presumably for an infinite time; and yet the humans in some sense consider themselves far ahead of the chicken, which will also be allowed to go on to infinity. Perhaps it is a question of greater "freedom" and range of actions and choices that one species can make.

DR. BOSSERT: I don't care to take it too far, but, in fact, what we do see here is a presentation of a strategy with respect to the use of the environment that one might not have expected. For example, an optimum strategy might be to cover the environment uniformly.

You see, in this last case the populations have arrayed themselves in a uniform pattern. Had we had six populations here, you would have seen them evolve a cluster in which the six populations achieved a uniform coverage of the subspace that they occupied in these two figures.

DR. MAYR: I think you ought to emphasize that is is a very specific case. This is reinforcement of isolating mechanisms.

DR. BOSSERT: Yes, I hope I began with that.

DR. LEVINS: Atrophic competition produces something quite similar.

DR. FENTRESS: I am still confused by the definition of fitness itself. This was the point raised earlier. It sounds as if you are speaking of fitness in an absolute sense. As a biologist, I am having trouble understanding what you are getting at.

The Chairman, DR. MEDAWAR: Dr. Bossert, could you possibly begin a sentence with the words "Fitness is," and proceed from there?

DR. BOSSERT: All right. Fitness is the relative probability of an individual giving offspring which will take part in the next reproductive population, or the relative numbers that an individual will add to the succeeding reproductive population.

DR. FENTRESS: How can you approach a certain level? This, I don't understand. You say that the animal is approaching a certain level of fitness, as if this were a fixed thing, but you could increase the number of offspring.

DR. BOSSERT: No, no, it is a relative thing.

DR. FENTRESS: You had the stagnation. The animal has been approaching something which I still don't understand.

DR. FRASER: It seems to me that he has W and S confounded in such a way that what he is really talking about is intrinsic rate of increase; and he is comparing them between points on a fitness space.

DR. EDEN: Dr. Bossert, let me see if I understand your model. You are saying that if you define two populations on one parameter with a distribution function on each, the region in which they overlap corresponds to hybridization in some sense. That is to say, where the populations overlap in a property, you don't know whether an element is a member of population A or population B.

DR. BOSSERT: Yes, except by the test of mating. The offspring will have viability depending on whether or not they are from a hybrid mating.

DR. EDEN: But where they don't overlap, they breed true, so to speak, either A or B, with whatever probabilities exist.

DR. BOSSERT: Yes.

DR. EDEN: Let me ask the question, then: Presumably, there must be some minimal distance between, let us say, the mean values of the populations which will push them apart through the selection mechanism which you have proposed; but there must be some threshold below which these two populations will fuse and become a single population; is that correct?

DR. BOSSERT: No, not in the examples I have given; because I have assumed that the offspring of these hybrid matings have negligible viability, so in fact they can never fuse. The other case is quite interesting but I don't think we should take time to go into it.

DR. WALTER HOWARD: Does your fitness have to do with successful breeding?

DR. BOSSERT: That is one component of it. All I am saying is that in this particular illustration, this component might have been considered separate from the additional components of the environment.

DR. HOWARD: But your figures are based entirely on that, your curves?

DR. BOSSERT: No, the curves are based on a combination of the two.

DR. LEVINS: First, when we talk about fitness it is always subject to certain constraints which are not always made explicit. Usually in population genetics we talk about optimization of fitness in the sense of finding a gene frequency from among the set of available alternatives which maximizes the fitness function. If you introduce new alleles from the outside, you change it completely.

In the same way, when you talk about phenotypic components of fitness, you can say that a heavy shell on an organism will make it resist certain kinds of predators better but a light shell will help it run away better; so, depending on the kind of situations that it faces, you can sort out adaptations and conflicts.

In the matter of protective coloration, then you have a new component of fitness in which the kinds of escape are not conflicting anymore; the whole surface is changed.

But what I would like to touch on is what I think is the real significance of Dr. Bossert's presentation. First of all, that selection can be extraordinarily slow and that, therefore, we are not justified in looking only at equilibrium phenomena when we talk about the maintenance of genetic variability. In fact, there must be a large number of situations in which there is quasi-equilibrium, populations stuck around the ridges or at saddle points. Secondly, the behavior of such a population, when it is displaced from a quasi equilibrium, will not be the same as that of a population displaced from a true equilibrium. At a true or stable equilibrium the population will return. When displaced from a quasi equilibrium, it could go on higher or do some other things that we don't really know; so this is a problem for the mathematician—the behavior around points of quasi equilibrium.

Third, the shape of this fitness space in which the points are moving depends very much on the way the phenotype is integrated in the development system. Roughly, strong interactions between genetic loci will give a very rough surface with lots of ridges. The simplest situations of additive effects just give you a simple sloping surface in which points can move quite easily. Therefore, high degrees of genetic epistasis between loci will produce systems remarkably resistant to natural selection, systems which will have very long memories and, therefore, would be important in higher order adaptive mechanisms.

Finally, I suggest that this may be the kind of situation that accounts for the anomalous observations of the Australian grasshopper, which is persistently hanging around on a point which is practically a minimum of its fitness surface.

DR. BOSSERT: May I first say that I think Dr. Levins was much too kind to attribute both of those points to my presentation. The second certainly was his.

DR. WADDINGTON: This business of displacement from a quasi equilibrium and then coming back not exactly to where you started from—this is surely the basis of

Sewall Wright's ideas. He displaces from a quasi equilibrium or sub-peak. He displaces by a small population sample, whereas here you are displacing by some determinate form of displacement.

DR. BOSSERT: I think it is important that this is not a sub-peak.

DR. WADDINGTON: This is a ridge; when there is an increase upwards it is exceedingly slow. You have quite steep fitness gradients going downward, but a very slow fitness gradient going up. The thing can't go fast until you go down; and then you get another rush at the hill and you come up to a different place. But surely this kind of thing is exactly what Sewall Wright was talking about in saying that if you got small enough population samples, you would be wandering around for purely statistical reasons and, therefore, would tend to come down a bit and then go up again a bit further.

DR. BOSSERT: In the examples given, the gradients on the slopes were several times the gradient up the ridge, but the differences in rate of movement of the population were much greater than this. The stagnation is due to the sharpness of the ridge rather than to the difference in selective gradients directly.

DR. LEVINS: This is different in the sense that in the average Sewall Wright case, the point returns toward the peak; selection is pulling it back toward the peak until it has gotten very far away. In that situation, even a very small displacement from the ridge will send it off in a different direction. Furthermore, because of the shape of the ridge, if a population has a large phenotypic variation, most of the selection is stabilizing, keeping it on the ridge, rather than sending it up the ridge.

DR. WADDINGTON: Yes, but you have invented the ridges. The ridges are the particular fitness surface you happen to have invented. You might have invented a different one.

There is a second point I want to make. This idea that there is a great deal of interaction and epistasis, in fact what I call canalization, gives you a rough fitness surface in which you can't wander about at liberty but have to follow the peaks and hills. This is the whole point, I think, of canalization; but Alex is shaking his head.

DR. FRASER: The idea that if you have got epistasis, then selection will be ineffective, has not been confirmed experimentally. When somebody decides to have a look in an experimental animal, he selects and finds that he is selecting on the basis of epistatic variants. This happens; it has happened too many times to be disregarded. You can simulate a genetic system in a machine where, by selecting for an optimum, you have put in a tremendous amount of epistasis, and obtain significant effects of selection. If there is fluctuation of population size—and I was quite intrigued by the deduction of the necessity for this by the second speaker this morning—your selection can be highly effective. We have selected in Drosophila, and had the whole of our advance being a first by third chromosome interaction, not an additive component change at all. To make statements that you can't play around with epistatic variants is not convincing. The statement that you have a highly flat fitness surface with a lot of little ridges in it is convincing.

DR. WALD: I would like a chance to ask a stupid question. With this as a definition of fitness, can any meaning be assigned to too great a reproductive success in one population over another?

DR. CROSBY: The point I would like to raise is, in a sense, complicating the issue of fitness. I have been working for some time on this question of hybridization, in a rather different way from the way in which Dr. Bossert has. The situation which is particularly interesting from the point of view of this discussion is the one in which the initial selection of the isolating factors is slow, and which has a maximum degree of overlap. Under those circumstances, the fitness is determined not by anything to do with the environment or with the genotype, but solely by the question of numbers; because under these circumstances the less frequent species is at a disadvantage.

Let's take species A and B; if A is less numerous, it will in fact produce proportionally more hybrids among its descendants than B. This means that unless the isolating factors are produced and established by

selection rather quickly, one of the two species is going to be wiped out.

We then have a rather pretty situation. Suppose for the moment B is the majority one; what you are saying is that its fitness will be increased if it develops isolating factors. This is not necessarily true; because its fittest position may be that in which it is able to wipe the other one out through hybridization.

DR. BOSSERT: You have brought up a very difficult thing. You have pointed out that there might be varying fitness over different overall complex strategies. For example, the strategy of resisting displacement might prove superior in some contexts. In the work I have done, the genetic mechanisms underlying the mating behavior were always identical in the various populations. So, what happens is that you find the smaller population being forced to move, or having selections for rapid movement. In that case, one finds further reduction in numbers in this rapid displacement to the point that even though the rapid displacement seems to be advantageous in that it decreases the relative number of hybrid matings, one finds it disadvantageous because one is selecting for individuals which have a very small probability of finding a mate at all, either A or B.

DR. CROSBY: In fact, the decrease in numbers is exponential. There is no question about it, it just shoots away, and selection cannot keep pace with it.

DR. BOSSERT: Yes, and I would predict that in most instances of displacement, one would find, in fact, the most rapidly displacing population becoming extinct.

DR. CROSBY: There is, in fact, a selective advantage to one species in being able to outhybridize the other, and I think this may well have happened a lot of times in the course of evolution.

DR. BARRICELLI: I have done some similar experiments together with Robert Toombs in Seattle, which in part are a repetition of experiments done by Jon Reed in Norway. They are based on the following: The method is basically the same as described by Dr. Bossert. Its purpose is to optimize self-reproducing numeric patterns using a high-speed computer. Each numeric pattern was composed of eight numbers comprising altogether 36 bits and which could therefore be stored in a single memory location of the IBM 7094 machine we were using. Four of the numbers are betting probabilities in a poker game, actually a very simplified version of a poker game in which each player received only one card, which could be either a high card (high hand) or a low card (low hand). There were 100 organisms or patterns and they played 20 games of poker, 50 organisms against the other 50. The losers were eliminated, and the winning organisms reproduced, so at the end of each generation we ended up with 100 organisms again.

The first number in each pattern (organism) was a crossing parameter; then we had a number representing the probability of betting high with high hand. Then we had the probability of betting low with low hand followed by the mutation probability. Then we had the probability of betting high with a low hand, and low with a low hand, and then we had a parameter regulating the mutation size. All of these numbers could be modified by mutations.

We did three experiments in this quantitative fashion. Incidentally, the optimum game strategy was calculated by Von Neumann's method, and we found that if the probability of receiving a high hand was 50 percent, the optimum game strategy would be always to bet high with high hands (probability 1 for betting high, 0 for betting low and 0 for passing), and always to bet low with low hands (probability 0 for betting high, 1 for betting low, and 0 for passing with a low hand).

In this particular case, when the probabilities of receiving high or low hands are 50% each, only the two extreme values of the betting probabilities—1 and 0—are compatible with optimum game strategy. We succeeded actually by the procedure described, in obtaining betting probabilities close to the optimum values within two or three hundred generations.

We have also used other probabilities for receiving a high hand. In some of these cases the optimal values of the betting prob-

abilities were not 1 or 0, but intermediate. This situation is more similar to the case presented by Dr. Bossert. We also observed the phenomenon Bossert has described, namely that the organism improved up to a certain point, which was not optimal. With different experiments we get different results which usually differ from the optimum betting probabilities.

The strange thing about all these experiments, which was observed first by Jon Reed, was that when we used crossing (either obligatory crossing or free crossing, meaning crossing regulated by the crossing parameter in each pattern) or no crossing at all, we got approximately the same speed of evolution. Crossing made no difference; Jon Reed was very surprised about that. Fortunately, we had already made some theory on a population genetic basis about evolution by quantitative characters. We expected that crossing would make no difference as long as one operates with quantitative characters only. We were therefore, able to explain Reed's result; however, this posed a challenge. What if we could repeat the experiments without using quantitative characters? If that were possible, one should expect a considerable enhancement of the speed of evolution produced by crossing, according to Fisher's law.

By a modification of the experimental arrangement we have been able to do just that. Instead of using betting probabilities which could have a continuous value, we used only the first bit in each betting parameter. If that bit was 1 in the parameter for betting high, the numeric organism would always bet high. If it was 0, then the machine would look at the first bit in the parameter for betting low; if that bit was 1, the organism would bet low; if it was 0, the organism would pass. This way we had defined a kind of Mendelian system, based on a few well-defined properties (such as the property of always betting high with high hand, or always betting low), rather than using intermediate probability values or quantitative characters. With this arrangement, crossing proved to enhance the speed of evolution in agreement with Fisher's Law. In other words, when we have four genes, or four bits controlling the betting probabilities as in our case, we get a speed of improvement about three-and-a-half times higher by allowing crossing than without crossing, which is fairly close to the result expected according to Fisher's Law.

Evolutionary Challenges to the Mathematical Interpretation of Evolution

DR. ERNST MAYR
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I came here under false pretenses, Victor Weisskopf's false pretenses. He said that I should be here at this conference on "Mathematical Challenges to the Neo-Darwinian Interpretation of Evolution" so that somebody would give a spirited response to the mathematicians. I tried to do that this morning. Then the next thing I noticed was that I was listed to give a talk myself; and in the hurry over the telephone I tentatively gave the title given in the program. But now that I have had more time to think about it, I have retitled my paper, "Evolutionary Challenges to the Mathematical Interpretation of Evolution."

We talked a lot this morning about parameters and the values of parameters, and there is no doubt that if we try the mathematical approach we have to know what parameters to accept. Those of you who know the literature from 1916-17 on, about when the concern with the quantitative aspects of evolution started, know that in the fifty years or so that have passed since the earliest papers, the parameters had to be changed all the time. For instance, in his early work, in order to prove that natural selection could produce evolution, Fisher assumed and accepted extraordinarily low values for differences in fitness. We now know that such low values are quite likely the exception and that we have extraordinarily strong differences in fitness under certain circumstances, in certain populations, in certain years or breeding seasons, etc.

I shall not go on with this particular line. All I want to say is that most of this research dealt only with two factors, mutation and selection, in other words, the original Darwinian model. Popper is right; this model is so good that it can explain everything, as Popper has rightly complained. Undoubtedly these two factors are necessary factors in any evolutionary model; but if we deal with more specific cases instead of Evolution as a whole (with a capital E), we have to think of additional factors and many of them have already been mentioned today.

Independently, I felt what Levins said this morning in the discussion: How about trying to get at this thing from the other side? Let me remind you of my title, "Evolutionary Challenges to the Mathematician." Let us start with some particular evolutionary situation and see, when we look backward, what this might suggest to us, what kinds of factors and what kinds of values of the parameters we must assume. Let me take just three kinds of evolutionary phenomena: evolutionary rates, rates of speciation, and rates of extinction, and see what we can find out.

Evolutionary rates. Let us begin with evolutionary rates. You all know that when pesticides were first tried—and the medical profession noticed the same about antibiotics—extraordinarily rapid rates of evolution were discovered. With Kettlewell in the audience, I hardly need remind you of the extraordinary evolution rates that were exhibited in the establishment of industrial melanism.

Last year a very interesting study (1) was published dealing with the evolution of the house sparrow (*Passer domesticus*), since its importation into the western world around 1850, 1853, 1856. In spite of all the transplantings, in spite of active dispersal,

the different local populations in Mexico, in British Columbia, in Hawaii, and at localities even closer together, became as different as populations in other species which every ornithologist calls different subspecies. It doesn't make any difference whether one studies size or pigmentation, an extraordinarily rapid rate of evolution is evident.

This is one side of the coin. Let's now turn it over and contemplate slow rates of evolution. You go to the paleontological literature and you read about Lingula or Limulus or other genera of marine invertebrates that have existed since the Cambrian, or Ordovician, or Silurian, for somewhat between 300 and 600 million years. Let's take one particular species, a freshwater fairy shrimp (*Triops cancriformis*), a very complex organism with extraordinary structural detail in its extremities. This species is known from the Triassic, a period of something like 180 or 200 million years ago. The Triassic form has been described as *minor* because it is a little smaller than the average of the modern population, but it agrees in all visible structural detail.

Let's now go to something else, Barghoorn's recent research on the pre-Cambrian organisms found in the cherts. There is a famous genus that Siegal has recently rediscovered as a living organism. This goes back, at least in generic form, to the gunflint cherts that are about 1.8 billion years old, without any essential change.

I heard of another case, still unpublished, of a blue green alga from some chert in Central Australia, (also work by Barghoorn and his students). This material is extraordinarily well preserved, so that the gelatinous sheath and every other detail is still clearly visible; and yet it is indistinguishable in all these details from a living species. However, the dating by the radioactive method indicates that this Australian form is 900 million years old.

The point I am trying to make is, to warn against being too rigid in our parameters. Here we have a case of a species not changing in 900 million years. In other cases like the house sparrow, we see very dramatic changes in a couple of years, certainly in less than 100 years. In the case of the blue green alga, of course, there is just the bare possibility—which I am not trying to minimize—that here we truly have an organism that has no cryptic gene exchange, no sexual mechanisms, no recombinational mechanisms of any kind. Blue green algae have been studied quite carefully and, so far as I know (I am not a botanist), no parasexual mechanism corresponding to what has been found in bacteria or fungi has ever been found. So much for rates of evolutionary change.

Rates of speciation. Now let's take a similar look at the process of speciation and again look at both sides of the coin. You all know by name Lake Victoria in East Africa, a huge lake with a rich fauna of fish. The most common genus is *Haplochromis,* one of the cichlids. I couldn't give you any exact number of the species found in Lake Victoria, but let's say about fifty; it may be seventy, but it is surely more than fifty. On the northwest side of Lake Victoria is a small lagoon, separated now by a ridge of sand dunes. That lake is about one square kilometer in size and six species of *Haplochromis* were found in this lake. One of them is identical with one of the species in Lake Victoria. Four of the other five are clearly related to four of the species in Lake Victoria, but sufficiently different in every way so that any self-respecting ichthyologist calls them different species. The fifth one is so different that, although it is probably related to one of these, the relationship is no longer perfectly obvious.

Now the question arises: How long ago did this lake become separated? How long did it take for the new species to evolve? If you go to "Dating the Past" of Zeuner, or to any of the other textbooks, the usual thing is to say that for new species (there is great variation) half a million or a million years is about the normal expectancy. It usually requires this long an isolation to produce a different species in higher vertebrates. I am not talking about polyploids or plants.

There are three methods, as I understand it, that were used to date the time at which this lake became separated: one, the usual radio-carbon procedure from wood found

buried in the dunes; second, another chemical method; and the usual quaternary geology method of determining the fluctuations in lake levels in connection with climate, limnology and pollen profiles. To make a long story short, the maximum age that the geologists allow the evolutionists for this lake is 5,000 years (2). The five endemic species of fish then evolved in this amazingly short time.

Now let's turn the coin over and take another geographic factor, take the barrier between the Caribbean and the Pacific, the Isthmus of Panama which connects Colombia with Central and North America; we know that there was an open arm of the sea where the isthmus is now. It used to be said that the last closing of the Panamanian gap happened about 2 million years ago. The most recent studies of Pleistocene geology and dating of the Pleistocene indicates that most likely this closing happened a little earlier. I would say that 5 million plus or minus is about as close a date as we can obtain on the basis of the available information.

If we look at the fauna of marine animals that were separated in the Caribbean and in the Pacific by this raising of the Isthmus of Panama and the closing of the Colombia Water Gap, we find that after these 5 million years in many cases differences are still either nonexistent or they are so slight that one doesn't really like to rank these as species.

Here we have two colossal gene pools; in the west, the whole coast of the Pacific and in the east, the whole Caribbean universe; while in the case of the African lake, you had a very, very small gene pool. This is a very crucial point of difference.

Rates of extinction. Now let me discuss a third type of phenomenon, a little more puzzling, even, than what I have discussed up to now, dealing with some recent work of mine. I plotted on double logarithmic paper the area of islands versus the percentage of endemic species of birds for each island.

DR. WEISSKOPF: What are endemic species?

DR. MAYR: Those that don't occur anywhere else. I found for three kinds of islands—truly isolated islands, islands that are members of archipelagos and islands that are close to continents or archipelagos —three curves. The range extended from the smallest islands up to New Caledonia and Madagascar, the largest that I included. If you had asked me before I did all this plotting what kind of curve I would expect, I would have said, I expect an increase up to, let's say, 300 square miles or perhaps 1,000 square miles and after that I expect the size to become immaterial and the curve to flatten out or to plateau.

It doesn't do that, but the analysis isn't completed yet and the whole interpretation is open to question. The interpretation which fits in with everything I have studied is that you have to start in your thinking with the largest island, which has the slowest turnover of its fauna. It is less affected by anything that comes in from the outside, less affected by extinction. It is a well-balanced universe and, therefore, it has a high percentage of endemic species that have lived there a long time, have radiated, and sometimes even produced endemic offspring.

However, the smaller the island gets, the more vulnerable the species are because the gene pools are smaller and can store less genetic variation. The less the genetic variation, the more likely they are to become extinct and therefore the lower the percentage of endemic species. In many small islands the turnover is so rapid that they harbor no endemic species at all.

The lesson of all three types of phenomena, as I see it (and I am not the first to say this), is that in addition to mutation, selection, and other well-known evolutionary factors, and superimposed on them, there is this tremendous importance of population size. Size of the gene pool has, in turn, a great influence on the interaction between genes, the cohesion of the total genotype.

Now let's take up a whole second theme and apply to it a similar set of ideas. To the nonspecialist, evolution always, somehow or other, means progressive evolution toward an ever greater perfection, like the horses in the Tertiary becoming more and more grassland animals with longer legs and

longer teeth, or the Hominid evolution trending toward ever greater brain size, or eye evolution leading to ever greater perfection of the eye. This really fits quite well the old *scala naturae* idea of the pre-nineteenth century philosophers and it is undoubtedly involved in all evolution; but it is only part of the story and maybe not the most important one in some ways. We have a second kind of evolution, which was referred to this morning and has cropped up again and again, also in Bossert's models here, which is what we might call "maintenance evolution." This is all kinds of stabilizing and normalizing selection that protect a species or a gene pool from genetic and evolutionary change, once that species or gene pool has acquired adequate adaptation to its environment. Much, if not most, natural selection is concerned with this maintenance evolution.

There is a third type of evolution which is very important, but even more difficult to handle than what we have considered up to now. This is what we might call "switch evolution," evolution in which, in the simplest case, an evolutionary line invades a new niche; or it might find its new niche to be the entrance to a whole new adaptive universe, a new adaptive zone. The first bird or pre-avis that was able to glide successfully from one tree to another was the beginning of the invasion of the wholly new adaptive universe of the aerial reptile. Anything that has to do with novelties, new adaptive zones, new niches, is accountable as switch evolution. Let me emphasize that, in a passive way, the continuous changes of the environment that we find, and which quite rightly were referred to all the time, results in a sort of combination between maintenance evolution and switch evolution. By wanting to maintain your adequate adaptation if the environment changes, you have got to switch to something new; but this is in a somewhat different sense from the picture of a pure switch evolution or pure maintenance evolution. The reason I am pointing this out is that the four phenomena that I am now discussing are not alternates. They almost always happen to proceed simultaneously.

The fourth one is, of course, speciation, the splitting of evolutionary lines, each line acquiring its own isolating mechanisms.

Now let's look at some of the evolutionary factors in the light of these four kinds of evolution. Let's take, for instance, genetic input into populations, into gene pools, into species. For the sake of simplicity the mathematical population geneticists more or less lumped together mutation and gene flow. This was completely legitimate in the early stages. Ultimately, all variation is, of course, due to mutation. One might consider gene flow simply as delayed mutation; but, actually, to the evolutionist, gene flow and mutation are two quite different things.

DR. WEISSKOPF: What is gene flow?

DR. MAYR: The movement of genes from one population to another. For instance, if the barrier between the little lake and the big lake is not complete, we would call gene flow all the genes that are transferred between the two lakes, owing to the movement of fishes.

QUESTION: Is it within one species?

DR. MAYR: It is normally within one species. Hybridization would be gene flow between species, and if the genes succeed, this is what Edgar Anderson refers to as introgression of genes from one species into another. In plants this is very important and in animals apparently less so.

Now, where is gene flow important? Where is mutation important? Where are they deleterious? In progressive evolution, high gene flow is desirable because every population may acquire some of these advantages that Ulam and Eden talked about. By gene flow they get carried to the next population and incorporated, so it helps in the spread of adaptive advance of the species as a whole.

In maintenance evolution it is equally important but for somewhat different reasons. Genes are lost all the time during reproduction owing to random elimination of genes in temporarily isolated small populations.

This is what Sewall Wright has emphasized so strongly. By gene flow these temporarily lost genes are restored and the population regains its heterogeneity, its whole set of canalizations and genetic homostases.

The important thing about gene flow is that it supplies pre-tested genes and gene combinations; natural selection in other populations has already worked on them. When they reach a new population they are already pre-tested, although as genotypes they may be slightly adjusted for some other locality and may not be perfect for the new locality. Yet, selection generally can handle this without difficulty. The input of untested new mutations in these cases would almost invariably have a deleterious effect.

In other situations exactly the opposite condition is important and advantageous: a cessation of gene flow. One situation is in switch evolution. If you are in the process of switching into a new adaptive zone you are (if I may use such anthropomorphic language), painfully building up the new gene complex that adapts for this new situation. To have it polluted all the time by genes from the parental gene pool pulls you back again to where you started from. This is very deleterious and we have now many such situations. This is why getting isolated in a little lake permits you to build up rather quickly, in fact very quickly, a new genotype, while in connection with a big gene pool this is an extremely slow process. Therefore, in both switch evolution and speciation it is a good thing to reduce gene flow. In fact, mutation under both circumstances is highly advantageous because it may give you just the kind of new genes that weren't previously there, the kind of genetic factors that permit either to build up isolating mechanisms, in the case of speciation, or to complete and improve adaptation, in the case of switch evolution.

In all of this (and I have said it many times), the importance of small population size comes to the fore again and again. Gulick, Hagedoorn, and Sewall Wright have emphasized the tremendous importance of small population size for evolution. For a long time, so far as I am concerned, they emphasized too much the stochastic aspects, the randomness aspects, random fixation and related phenomena. It is now becoming very clear—and I think I was probably the first one really to emphasize this in my 1954 paper—that in small populations certain selection phenomena are possible that are not possible in large populations. A whole set of things may happen.

If you look at genes, there is an indication that there are different kinds of genes. This is probable even though we have no real proof. Even taking ordinary enzyme-producing genes, some are especially important in allelic combinations and in particular allelic combinations; however, they perform very poorly in other combinations. At the same time other genes in the same genotype have their greatest advantage in that they are doing well in a great many different epistatic combinations. When you have a big populous species with a great deal of gene flow, a great deal of mixing of genotypes, certain genes are more advantageous than when you have a small, isolated population with a great deal of homozygosity as the result of inbreeding.

It is in these small populations that you have a chance by this extreme inbreeding, or at least a certain amount of inbreeding, to get what Lerner years ago described as genetic deviants, phenotypic deviants. The canalization and the homeostatic mechanisms seem to break down owing to increased or extreme homozygosis: and the changes in the phenotype that happen under these circumstances give selection a new handle by which it can do things that it cannot do in large gene pools. Furthermore, locally isolated populations can respond to local selection pressures, while previously they couldn't; because they had to continuously absorb all the gene flow from the remainder of the species population.

These considerations of time, of space, of population size, result in an emerging picture of evolution which is in some respects, and particularly in emphasis, somewhat different from the classical neo-Darwinian picture that we find in the literature. I want to say that when the mathematicians this morning talked about the neo-Darwinian model, they talked about Fisher of 1930 and Sewall Wright of 1931. The people who are now most active in the evolutionary field have by no means abandoned what Fisher, Haldane and Sewall Wright said but, they have built on it a lot

of additional superstructure. Therefore, the neo-Darwinian story, what is it, really? Is it what Fisher and Wright said 35 years ago or what we believe in 1966?

The new picture indicates that every once in a while a new species originates that has a highly successful genotype. It can spread widely, become very populous, and can continue to improve slightly by progressive evolution. But once it reaches its adaptive peak, it will be subject primarily to maintenance evolution. When a species reaches the status of a successful widespread populous species, it seems that it becomes rather incapable of undertaking major switches or acquiring major evolutionary novelties. It is also unable to speciate, at least within the main body of the species.

I might say the widespread populous species is what the paleontologist usually finds in a fossil deposit simply as a matter of chance. Much of evolutionary theory that we have learned from paleontology is quite true for widespread populous species but this doesn't give us a complete picture of evolution. In fact, it has in a way almost falsified the picture.

In contrast to the widespread populous species is the second kind of species consisting of many small, more or less isolated populations, most of them being peripheral geographic isolates separated from a more contiguous set of populations in the core of the species. Owing to all sorts of genetic indeterminacies, including the founder principle, and owing to the various factors previously outlined, such isolated populations can undergo a great deal of genetic change in a very short time. They can acquire new isolating mechanisms and experiment with new kinds of niche utilization and the invasion of new adaptive zones. The vast majority of these experiments are unsuccessful, just as the vast majority of all mutations leave no lasting evolutionary effects; yet the occasional evolutionary experiment is successful and evolutionary advance is made. Sometimes this leads to the replacement of one of the previously successful species. In other cases, the new evolutionary line finds a previously unoccupied ecological niche or adaptive zone and it can spread without greatly disturbing the existing organic universe.

To me, as an evolutionist, the greatest advantage of computer simulation is the fact that the computer can simulate such a wide range of possible conditions. If there is anything we have learned in the last twenty-five years, it is that evolution is a remarkably diversified phenomenon. I refer to the various things I have mentioned earlier. Evolution is the change of systems, the modification of one extremely complex system under the impact of extremely complex sets of selective and random forces into a different one; and I doubt that simplistic, deterministic models will give us a realistic picture of evolutionary events.

In my recent book I set aside an entire chapter to discuss the unity of the genotype, and this is something I think Ulam and I referred to this morning. You cannot separate genes out; you cannot expose *a gene* to selection. The whole organism (phenotype) responds to the selection as a whole. Many nonspecialists still tend to think, as did the early Mendelians, that each gene controls a particular component of the phenotype and that for all practical purposes it doesn't really make very much difference whether one talks about the genotype or the phenotype.

Now we know what Waddington has quite correctly stressed for many decades, that the simple gene products, the enzymes or whatever they might be in each case, interact with each other in countless ways during development and regulation. We know that the epigenotype, as Waddington has called it, is a single interdependent whole. This observation is important on all levels of biology. If an enzyme has 100 amino acid residues and the active site is occupied by only 8 residues, it does not mean that the other 92 are irrelevant. They are not "noise", as the information theorists might call it, or "garbage," as one biochemist once said.

It is now quite evident that these other 92 sites (and again I am repeating something that was said in the discussion this morning) have to do with the folding of the molecule which, in turn, affects the

interactions of the molecule with others and also facilitates the operations of the active site. Just how important such interaction is, is demonstrated by the constancy of molecules in the major types of organisms. In so much of our discussion we have emphasized the changes, the mutations, but in some ways we learn more about these macromolecules by looking at their constancy.

In spite of the enormous mutation pressure—just recall the right-hand side of Ulam's tabulation this morning—there is, for instance, so far as we know, total constancy on all 103 sites (I have taken this figure from memory and it may not be completely correct) of the cytochrome C molecule in the entire order of ungulates. Admittedly only three or four scattered species have actually been analyzed by now. What does this mean? It means, of course, there must have been a steady mutation pressure all the time, affecting millions of individuals for hundreds of species for millions of generations. Yet any change at any of the places in the DNA code, where it produced a change in the amino acid sequence, any such mutation was selected against. Therefore, it shows how important every smallest detail of the molecule is and how natural selection continuously controls this.

The interaction of genes is more and more recognized as one of the great evolutionary factors. The longer a genotype is maintained in evolution, the stronger will its developmental homeostasis, its canalizations, its system of internal feedbacks, become. The stronger such an internal cohesion is, the more the genotype will respond to selection pressures as a whole rather than as an aggregate of individual genes.

I am referring back to the evolutionary lines that have remained essentially unchanged for 50, 100, 200 or 900 millions of years. As long as evolutionists did not make the clear distinction between genotype and phenotype, such evolutionary constancy was explained in terms of low mutation rates or low selection pressures. As soon as one adopts the model of the internally balanced, almost totally homeostatic genotype, one can justify evolutionary constancy in the presence of normal mutation and selection rates.

As I pointed out recently (3), one of the real puzzles of evolution is how to break up such a perfectly co-adapted system in such a way so as not to induce extinction; in most cases it results in extinction. We do know that such a loosening up occurs occasionally, leading to unexpected and highly dramatic, but usually very temporary, diversification of phenotypes. This phenomenon evolutionists have referred to as explosive evolution (usually combined with adaptive radiation). Cases are known from paleontology in which for 50 or 100 million years a genus stayed unchanging until all of a sudden it burst out into twelve, fifteen, twenty-five descendant genera. After, geologically speaking, a relatively short time span, such evolutionary lines usually undergo a period of heavy extinction and then return to the previously existing stability.

The reason I stress this phenomenon is to emphasize that in a realistic model of evolution we cannot deal with each gene locus as an isolated phenomenon. It is a gross exaggeration to claim that every character of an organism is affected by all genes and that every gene affects all characters. Yet this statement is perhaps closer to the truth than the belief of the early Mendelians of the organism as an aggregate of genes, each of which could be substituted without any other effects, except on that one component of the phenotype controlled by the particular gene locus.

The terms "uniqueness" and "quality" were given in the title of my contribution as originally announced on the program. It should be clear by now what I meant by these two words. Every individual in sexually reproducing species is genetically unique, but this is not nearly as important for evolution as the fact that every population is likewise unique. It is this uniqueness of populations, whether they be populations of a single species or whether they be different species, which is such an important determinant of evolution. As Lewontin (4) has recently pointed out, the effect of a

given selection pressure is largely determined by the kind of selection that had preceded it. In our consideration of uniqueness, we must never lose sight of the fact that organisms are historical beings, that their genetic programs are the result of an historical process of selection, and that the particular unity of the genotype of a particular species or population was arrived at through a sequence of steps. It is, in part, *this very sequence* which determines the quality of this genotype.

With quality so important, let me say a few more words about the problem of quality. This is a component that is not at all easily expressed, mathematically or otherwise. This is why the early population geneticists, and quite rightly so, emphasized events and processes that could be expressed quantitatively. Quality, unhappily, is something rather elusive, particularly if it is not due to unit factors but due to a complex epistatic interaction of the total genotype. Yet I feel that we cannot afford to adopt an ostrich policy and simply ignore the phenomenon of quality. The evolutionist has never done this, and if he speaks of "high selective value" or "low selective value," or "highly adapted" or "poorly adapted," he is obviously referring to quality. Yet we have never gone out of our way to study the effects of quality or change of quality. I think Waddington will devote some of his time to a discussion of this topic and I will say no more.

All I want to say at this point is that the simple arithmetic approach, the simple prediction that if gene A has a value of 2 and gene B a value of 3 and gene C a value of 5, bringing them together will give us a value of 10, just simply isn't true. Bringing them together may have a deleterious effect or it may result in a quantum jump of adaptive improvement. The breeders of hybrid corn have realized this for a long time in their search for high combining qualities of their inbred strains.

What does all this mean to him who wants to simulate evolution with the help of the computer? I think it should mean one thing in particular, which is that the approach adopted should not be too simplistic. To be sure, one will have to start with a set of simplified assumptions and expand from them gradually; but in the end one would have to adopt for every set of factors a far greater range of extremes than was believed necessary or even possible only twenty years ago. Evolution, again and again, has resulted in unique phenomena and in startlingly unpredictable phenomena. If we set up our programs in too deterministic a manner, I am afraid we will never be able to arrive at a realistic interpretation of evolution.

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Discussion

PAPER BY DR. MAYR

The Chairman, DR. MEDAWAR: Thank you very much, indeed, Dr. Mayr. I think it will best fulfill the purpose of this conference if the discussion is opened by our mathematical friends and we will let them have the floor.

DR. EDEN: Let me make a comment and then ask a rather simple question. The comment is that about two months ago Dr. Kaplan asked me to put my money where my mouth is and I began to try to pull together my ideas. In the course of which time

I had a chance to meet with Dr. Bossert and during our conversation he made the following remark. "You can be sure that no matter what you may say, Dr. Mayr has already anticipated you in writing."

As a matter of fact, as I sat here listening to Dr. Mayr, trying to make a translation from the language he uses to the mathematical language that is more familiar to me, I found we really have no serious disagreement as to what the problems here are. I welcome the fact that he has turned the theme of the meeting upside down and suggested that there are evolutionary challenges to mathematics. That, precisely, is the point. I feel that some of the problems he has pointed out are, indeed, amenable to mathematical treatment, simulation, or whatnot.

I might make one additional comment about simulation which attempts to imitate what looks like a complicated biological phenomenon with a relatively simple computer program.

There is a botanist currently in our group, Dr. Dan Cohen of the Hebrew University, who has attempted to write an algorithm for generating venation patterns. The venation patterns are restricted to two dimensions because it is hard to visualize them in three. The program itself is a relatively simple one; it probably doesn't take more than about a thousand instructions. The notion behind it is very simple. One starts with a "stalk" and one applies certain rules weighted probabilistically as to where the stalk will branch, what angle the new branchings will take, etc. One iterates the process a number of times introducing certain factors—the effect of gravitation or the effect of having too dense a population of twigs in one place or another.

From the point of view of the computer, a 1,000-instruction program is a very simple one. Further, with rather minor variations in the parameters of the program, one can develop objects that look to my eye as a willow tree, or a fir tree, or a variety of other forms, that are quite distinct at a qualitative level. Nonetheless, on the mathematical level they involve nothing more than minor variations in parameters.

What I am attempting to point out is that when one has an algorithmic description of a process that looks complicated to the naked eye, the algorithm itself may prescribe the process in a very simple way.

The question I want to ask is a rather minor one. I was interested in your story about these organisms that are stable over many millions of years. If we take the blue green algae, which have changed little, if any, in a billion years, it is my impression that the salinity of the ocean has been increasing steadily since oceans were first formed. If we assume it is linear, then presumably in the last billion years the salinity has changed by a factor of 25 percent or so. You have speculated, to my lights, rather well earlier. I wonder if you would speculate on that—on what blue green algae did about the salinity of the ocean.

DR. MAYR: It is possible the facts will save me on this one so that I don't have to speculate. Most of these blue green algae live in fresh water. I think these particular cherts, if I am not mistaken, are from fresh water deposits, so there is no question.

DR. SCHUTZENBERGER: You hinted that the stability was concerned with size, that a very large size gene pool was advantageous. Is it a possibility in some cases or is it what you consider a general explanation?

DR. MAYR: Looking at it from the gene pool toward the organism, I think there is a good deal of evidence (Haldane even expressed it mathematically) that the larger your gene pool, the more difficult it becomes—or at least the more time it takes—to replace one gene by another, even if it has selective advantage. The larger the gene pool the greater apparently the genetic (evolutionary) inertia. This is not the same as genetic homeostasis but it is a somewhat related phenomenon. Mind you, this again is speculation. Let's say a mutation occurs in the hemoglobin molecule which may be advantageous for functions of the hemoglobin but is not advantageous in some other part of the organism. It is likely that the genotype will incorporate a gene from somewhere else that will cover up, so to speak, the part of the hemoglobin's phenotypic effect that is disadvantageous. So the

system as a whole stays superficially the same.

We know groups of species in Drosophila and in many other organisms in which speciation has been very active. The resulting new species are reproductively isolated, are completely sterile with each other and may have changes in chromosomes; and yet morphologically they haven't changed in any appreciable way. Again the feeling one has is that to make any changes in the morphology of the phenotype, in the canalizations, in the developmental pathways, and all that, would create a good deal of disturbance. It seems much easier to cover up all the side effects of the genes that are selected for isolating mechanisms and whatnot and to leave the old phenotype otherwise as untouched as possible. This all sounds very anthropomorphic, but you can set it up in a perfectly objective way.

If an organism goes through a bottleneck of a very small population, somehow or other, again and again, we find that certainly something happens to the whole genetic system. We can only infer that something happens to the genotype, but we can see that something happens to the phenotype; and then the organism can go off in a whole new direction, obeying new selection pressures.

DR. SCHUTZENBERGER: I was just puzzled. You gave very striking examples of the possibilities of arrays of speciation, and I was wondering if it was your general explanation that slowness of rate, as with certain fossils, was due to it. The Sphénodon is not so popular.

DR. MAYR: Of course, it still has the characters of that particular order of reptiles, but it may be quite different from the old Sphénodon ancestor in the Mesozoic. It has one thing in common with it (and this is only inferred)—certain physiological adaptations, namely, its temperature regulation—which makes it inferior in places where it is exposed to competition from other lines. But as long as it is in New Zealand, or in the little islands off New Zealand, it is safe. I wouldn't say that always a relatively small population must, necessarily, change all the time. You could, of course, say, "Well, if the large one always stays very much the same, then the small one will always change greatly."

All I claim is that when a small population is split off from a large population, it goes through a bottleneck of drastically changing size of the gene pool and then breaks out of it again. This almost invariably will be connected with a reconstruction, not just of the genotype but also of the phenotype. In the case of a population that is permanently of small population size, I think if there are enough stabilizing selection factors trying to maintain the phenotype, it could well stay that way for a long time without changing. Size of population is, perhaps, not as important as changes in the size of the gene pool.

DR. ULAM: As you said, the whole story is of a fantastic richness and complexity, but still it might be worthwhile to think of some terribly simplified models just to get the possibility of some coherent conversation about it. Some of the simplest questions, which come to mind to anyone interested in the universe of living things, are of a yes or no nature. As we have discussed it before, a layman like myself, or some mathematicians at any rate, are curious to know whether in the time of one billion years the mechanisms proposed by the theory of random mutation and survival of the fittest were sufficient to produce the present-day life. Some quantitative discussions of such processes are worth imitating mechanically. As for myself, I must say that I believe that such quantitative discussions are beginning to be possible. Do you think that it makes sense to even start such speculations?

DR. MAYR: Nobody knows any answer; but let me say just one thing. If for your Kappa you would put down 10 million instead of putting down 10,000 it would not scare me. Because, at all the other levels, the richness of gene pools, the tremendous selective advantages of the buffer gene combinations, the frequency of mutations, the extraordinary amount of gene flow, work in the opposite direction. These are aspects that do not come out in the genetic literature; but take a local population, an interbreeding local population and measure the input of new genes in each generation. (This used always to be thought of in terms

of mutation, how many mutations happened there.) Actually, if you took an input of 100 genes, new genes that weren't there before, 99 would have come in by gene flow and only one by mutation. The conditions are all given which would permit you to make a lot of changes, let's say 10 million changes in 100 million years, without bothering your system, particularly.

DR. ULAM: Yes, but at the time when only pre-bacteria existed, all this was presumably much more difficult.

DR. MAYR: The latest indirect evidence is that life started, of course, quite a bit earlier than we had thought. There is now suggestive evidence for life at well more than 2 billion years ago; some have made claims for as far back as 3.2 billion years. Another thing that is usually overlooked (and I think that all the microbiologists agree) is that mechanisms for genetic recombination came in almost simultaneously with life itself. It is, as you pointed out, a thing of such tremendous selective advantage that anything that would allow two lines to exchange factors that will help them to work on a substrate that would otherwise not be acceptable, of course, will be selected for. So, I think mechanisms for recombinations, in other words, sexuality in the broadest sense of the word, go just about as far back as life itself.

There is another way to approach this problem. Let us make some extremely simplified assumptions, to get somewhere near the right order of magnitude. Let us say that 300 is the average number of amino acid residues per gene-controlled enzyme. Let us say that between the lowest procaryotes and the highest mammal there have been 500 mutational changes per gene (including successive changes). Let us also say that higher mammals have 5 million mutating genes (by no means all going back to the pro-caryotes!). Before we know it, we come awfully close to 1 billion mutational steps between pro-caryotes and us. Therefore 10 million or 50 million would certainly not seem excessive estimates, unless there is far greater heterogeneity in the nature of cistrons than we realize.

The Chairman, DR. MEDAWAR: Dr. Bossert, would you like to say something?

DR. BOSSERT: No, I was quite happy that so many of the ideas I tried to bring up were finished off so beautifully by Professor Mayr.

DR. ZIRKLE: I would like to add a botanical example to the fact you brought out, that a large population will evolve very slowly. The example lies in the well-known fact that windborne pollen from a large population may swamp what would otherwise be fit variations, thus destroying much of the raw material for evolution. As you know, a cultivated variety represents a hazard that will often cause its wild ancestor to become extinct. A cultivated variety as selected by man, such as our Indian corn, often cannot take care of itself; but the pollen it produces carries its genes over to the wild ancestor. Thus, deleterious genes accumulate in the wild ancestor until it becomes extinct.

DR. WALD: There is something that troubles me a little about what you were saying. If you are dealing with a small population and a small gene pool, I can well understand how it might change more rapidly than a large one and become extinct or change as a whole; but I don't quite understand the mechanisms by which it radiates into five or six different lines. It would seem to me that radiation would be easier in a big population.

DR. MAYR: Of course, one small gene pool doesn't radiate into many lines. I think the language I used must have been misleading. Let us simply start with the case of a single species having a series of peripheral isolates. Of course, each isolate can specialize in a different way as shown by many examples. For instance, certain insects that are host specific may live on host A, but they can just manage to get by on some other host. Then in isolated sub-populations these species do live on other hosts such as B, C, D and E. Each of these isolates after a while also acquires isolating mechanisms and then when they return to the central geographic area each of these five species lives on a different host and at the same time is reproductively isolated from the parent population.

I have discussed this on the level of speciation but now let's go to the level of

full species. We may have an evolutionary line which did not change for 100 million years and then all of a sudden, at a particular point, it radiates into a highly diverse set of new evolutionary lines. Nobody yet understands why this can happen; it may have to do with going through a small population bottleneck, or hybridization may disrupt the cohesion of the genotype, or goodness knows what—this line suddenly starts to speciate. As a result, you now have eight or ten full species, each one adapted to a somewhat different niche.

Once the tight canalization has been loosened up and thoroughly disrupted, the descendant lines can go off into all sorts of new directions; although this is nothing but a model, it fits the known facts.

Since their genotype was so recently loosened up, they are undergoing an exceedingly rapid genetic reconstruction to adapt themselves to the new environment and to the competition from all the other lines that are so closely related to them.

Whenever a major new evolutionary branch originates, whether the birds or the first mammals, or any other major new taxon, it always goes in an incredibly short time (geologically speaking) through that labile stage between the well-defined ancestral phenotype and the new descendant type. This is what was such a puzzle to Goldschmidt. He assumed that evolutionary rates were essentially constant and therefore he had to postulate major saltations ("systemic mutations") in order to avoid absurd conclusions. For if one would take the extremely slow rate of evolution of the bats from the Eocene to the present as the standard rate of this phyletic line, one would, by backward extrapolation, require all the time to the beginning of the earth to get even as far as the Reptiles. The basic error is to believe in standard rates. Actually, the rate of evolution in any phyletic line is subject to tremendous change.

When the first insectivore went into trees and jumped and started to flutter, it went through that transitional stage, quite likely in a period of a few million years. However, once the bat stage had been reached 65 million years ago, very little new has happened. An Eocene bat looks just like a modern bat. So, I think that during this stage of the reshuffling of the genotype, all sorts of things can happen that cannot happen before nor afterwards.

DR. HOWARD: I want to ask for clarification of two points. You were speaking about the genetic resistance that has resulted as a consequence of the use of pesticides. Is this what you referred to as rapid evolution?

DR. MAYR: This is a case of sudden change in environment. I wanted to emphasize the rapidity. Within less than two years houseflies in Sweden and some other areas had become completely resistant to DDT.

DR. HOWARD: But, isn't it possible that Triops, and some of the other species which have remained constant for so long, also may have had that same degree of change in gene frequency many times in their paleontological periods, even though it has never been observed?

DR. MAYR: You are quite right. They may have undergone similar changes and we would never have known it.

The Problems of Vicarious Selection

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When Dr. Kaplan invited me to attend this meeting on "Mathematical Challenges to the Neo-Darwinian Interpretation of Evolution," I told him that I would be delighted to come and expected to learn a great deal from the discussion; but of course I could not think of presenting a paper in a field so remote from my own. When I learned with some dismay from one of his later communications that I had been scheduled nevertheless to give a paper, my first impulse was to remind him at once of what I thought to have been our agreement. On second thought, however, I realized that I had a problem in this area that I had never seen discussed (though I would be most surprised if it has not had a thorough discussion in a literature unfamiliar to me). So what I have to offer is primarily a problem; yet, I think, a problem that comes with at least the germ of its solution.

The problem is very general indeed, and I have encountered it in a great variety of ways. Any one of these will serve almost equally well to introduce it.

Many years ago I had an experience that demonstrated in a striking way how fish in the oceans can continue to see at depths below those to which sunlight penetrates, and indeed continue to see at night. A fellow graduate student, now Professor Harry Grundfest, had come to Woods Hole to set up experiments on the vision of fishes. Our chief, Selig Hecht, had provided him with what looked to be a fine dark room. When Grundfest had set everything up and was ready to begin work, he noticed with surprise that he could see the fish in his apparatus, though he had not turned on the light. For a few days he went about the room trying to stopper up possible light leaks; but finally he realized that there was no light leak and that in fact he was seeing the fish because it was coated with luminescent bacteria. It seems that most objects, living and otherwise, are quite generally coated with luminescent bacteria in the depths of the ocean, and are thereby made visible. This seems clearly to be highly advantageous for fishes. What, however, does it do for the bacteria?

By now we can pursue this question into further subtleties. Some years ago I examined the visual pigment in the retinas of a variety of marine fishes, and found it to be the conventional rhodopsin, with maximum absorption at about 500 mμ (1). Years later, Eric Denton at the Plymouth Laboratory in England discovered that fish taken from the depths—below two hundred meters—have what came to be called deep-sea rhodopsin, the maximum absorption of which has slipped over to about 480 mμ (2). My first fishes had habitats near the surface. It turned out on further examination that there is a rough correlation between the depths frequented by fishes and the wavelength of maximum absorption of their visual pigments. The limit seems to be reached below about 200 meters, where the maximum absorption of the visual pigment is near 480 mμ (3).

This is however just about the wavelength of deepest penetration of sunlight. At 200-250 meters depth in the ocean, the entire spectrum of sunlight has been reduced to a narrow band of blue light (450-505 mμ), centering at about 480 mμ (4). "Deep-sea rhodopsin" seems to be an adap-

tation to this wavelength of deepest penetration of sunlight.

At still lower depths fish have to rely upon bioluminescence, particularly bacterial bioluminescence, to go on seeing. Careful measurements have been made of the spectral emission of a variety of such bacteria; and the remarkable fact emerges that it tends very strongly to peak in the same spectral region (490-505 $m\mu$). I am sure that exceptions to this rule occur, but the rule holds remarkably well (5 & 6).

So we see that these luminescent bacteria not only provide light helpful to fishes, but go the further length of providing it at the most advantageous wavelength. I think one would be hard put to argue that their luminescence does anything directly for the bacteria. On the contrary, it costs them a good deal in substance, energy sources, and metabolism to produce light. It seems to me that if an advantage accrues to bacteria—and one would be inclined to postulate such an advantage for the phenomenon to have arisen and persisted and indeed become very general—then it must come from the complex of mutual relationships that involve the creatures sharing the deep-sea environment. It seems to me that once the problem is put that way, the answer is reasonably clear. It would seem rather obviously to be of great advantage to bacteria in the deep sea that fish prosper. The more fish, living and dead, and the more excretory and decay products from fish, the more substrate for bacteria. It does not therefore seem astonishing to me that bacteria have developed this elaborate adaptation of no use to them directly, but of great eventual advantage through being highly advantageous to fish.

Such relationships can ramify further. Granted that it may be of mutual advantage for bacteria to luminesce so that fish can see, once certain bacteria have begun to provide light, it becomes even more advantageous for other bacteria to remain dark. They would in that way have just as much access to the fish, while sparing themselves the metabolic burden of bioluminescence. Yet in spite of that competitive advantage, dark bacteria could ill afford to replace the luminescent forms, for then all would suffer from the light going out. Similarly, a deep-sea environment lighted by luminous bacteria is of general advantage to fish, yet would seem to offer a special advantage to fish which themselves manage to remain dark. Here again the ultimate selective advantage lies in keeping intact the mutually beneficial condition even while exploiting it unilaterally. It would seem that the type of phenomenon I am discussing might tend to have that result.

This rather esoteric example will help to introduce what I think to be a very general type of relationship. It comes at us in all kinds of ways. For example, how can worker bees have developed their extraordinary patterns of behavior—the hive-building, the search patterns, the "language," the swarming behavior—though the animals engaged in all these activities are sterile females? Quite clearly in this instance the hive of bees represents an organism of higher order than the individual bee. Natural selection operates upon the society of bees, in competition with other bee societies and with other types of living creatures. The germinal material in the queen and drones represents the hive as a whole and survives or fails depending upon the effectiveness of the whole society, which is based most of all upon the performance of the sterile worker bees.

Here we have, therefore, essentially the same principle in operation. It may already have a name, but in my ignorance I shall call it "vicarious selection." In the first instance no social organization is involved, but only the operation of what I think is called an "ecosystem"—the complex net of relationships that involves any group of living organisms occupying the same territory. In the second instance we have to do with the much more direct system of relationships that involves a highly organized animal society, composed of a single species.

The latter, social type of relationship, comes much closer to home. I have been much interested lately in developing a set of thoughts involving the realization that death in multicellular organisms involves the discarding of the soma after its principal function, the fostering of the germ

plasm, has been completed with the act of reproduction. In many types of animals—salmon, eels, lampreys—the preparation for reproduction is simultaneously a preparation for death. The act of reproduction is the last act of life, and the animal—having, for example, suffered a complete collapse of its digestive system—is incapable of living beyond it. In this connection the question arose, is life always finished with organisms once the reproductive act has been accomplished?

The answer obviously is no, not if, for example, one is dealing with socially organized organisms; for in them, services to the society can represent a great and continuing advantage quite apart from the act of reproduction. Worker bees are a fine example of that; but men and women in human societies, individuals who may never take part in reproduction, or who have passed the reproductive period, can perform services that represent obvious advantages to their society as a whole, and hence to its reproductive members. It seems to me, therefore, that here is a mechanism such as is sometimes denied, for the selection of characters that exist in individuals who themselves do not reproduce.

To the degree that such vicarious selection is effective in a society, it will operate to promote the increasing effectiveness of of its non-reproducing members. In human society, for example, that would involve not only selection for superior performance in its non-reproducing members, but, to the degree that older persons provide reproductive advantages for younger members of the society, it might involve a selection for longevity.

I am assuming here that traits transmitted from generation to generation by teaching and imitation—learned behavior, culture—have a comparable status with genetic inheritance as a basis for natural selection. Indeed it is often difficult to tell with which type of inheritance one is dealing—genetic or cultural, nature or nurture. Often it is a mixture of both, in which nature and nurture have the relations of an independent and dependent variable: genetics provides the substrate that is exploited through culture. So, for example, language and hand skills are acquired characters, yet built upon the congenital structures of the human hand and mouth parts, as also upon a striking over-development of the sensory and motor areas of the cerebral cortex connected with the mouth and hand.

All of this seems rather obvious to me. I think that running through all such situations is the recognition that a body of germinal material reflects in its evolution all the forces, however external, that have promoted its survival. Those forces can be as remote as involving the prosperity of wholly different orders of organisms, or can come closer and involve the performance of fellow members of a relatively small social group. In any case, for this type of relationship to work, the advantage must be mutual. A genetic variation in A must not only benefit B, but to be selected must also redound to the ultimate advantage of A.

In this sense, however, is not all selection vicarious? The germ plasm as the bearer of heredity and ultimately therefore of evolution, ordinarily takes no part in the struggle for existence. Indeed, it is elaborately protected from all the eventualities that compose that struggle. It is represented in that struggle by the soma, another body of cells that engages in the competition for survival; and the germ plasm endures or fails depending upon how effectively the soma has represented it. Clearly there is no great gap in principle between this dependence of the germ plasm upon its own soma in the struggle for survival and extending that dependence to another soma, whether of the same species or perhaps of a very different species. Once the conditions of mutual advantage are established, the systematic relationship is irrelevant.

Perhaps there is, therefore, no occasion for surprise in finding organisms highly and subtly adapted in ways that seem to represent no direct advantage, yet offer an ultimate advantage through their effects upon other organisms. Such evolution by proxy would seem to be a very general phenomenon, and its mechanisms may merit more attention than they seem as yet to have received.

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Discussion

PAPER BY DR. WALD

DR. CARLETON S. COON: As for the parallel between bees and people, a Jesuit can always be unfrocked and produce a family afterwards, while you can't unfrock a worker bee.

DR. WALD: The unfrocked Jesuit is an evasion of my question. The point is, can Jesuits be selected for, so to speak; can a society that includes Jesuits be selected for even if they don't father any children?

DR. LEVINS: What is being selected for is not the survival of the individual but of the genes. If the action of an individual increases the survival of its own genes, this may be representative of the genes of his offspring or of his brother which are selected. It may be desirable for bacteria, in general, that fish prosper; but this is equally good for the bacteria who are luminous or nonluminous, if it involves fish in general. If, however, the particular offspring of the bacteria will have a greater survival because they are on a fish which glows, then there is this correlation of parent to offspring which allows selection to operate.

In those groups in which there is triploidy, for instance, the parent-offspring correlation can be very much stronger and, therefore, you might find even greater selection for parental care. It is the relation, then, between the genotypes of related individuals and those unrelated which determines whether this kind of selection will work.

DR. WALD: Yes, I am quite aware of the point you have made; and of course this working paper raises a further question: Isn't all selection vicarious in a sense, in precisely the sense that it is not germinal material that engages in the struggle for existence? On the contrary, it is being represented by an entirely different body of cells, the soma, and once one grants that, why not extend it?

As for your point about the fact that luminous bacteria will, so to speak, provide an even greater advantage for dark bacteria, since they don't have to work to provide light, let me say yes; but I thought about that and one would be in a curious bind. So long as there are lots of luminous bacteria it is even an advantage to be nonluminous, and still feed on the fish. If the dark bacteria exploit that advantage by displacing the luminous ones, however, all of them lose through the light going out; so the bacteria have to be careful.

DR. ULAM: I want to say again that there is a difference between (a) the probability of an acquisition of an entirely new characteristic, such as the ability to luminesce or produce a new enzyme; this is connected with something I called α; (b) the selective advantage connected with γ refers to another point, namely how useful such a new characteristic is once it is there, and then how quickly it establishes itself in

the majority of a given population. These are two different things.

What intrigues laymen and specialists alike is, of course, how all this great process started. Are the mutations and the selective advantages enough to explain the developments or does one need other mechanisms, e.g. transductions, development through feedbacks into genes during the lifetime of an individual etc.?

DR. SCHUTZENBERGER: I should like to ask a question of a methodological nature. Under which principle can you exclude the fact that European eels have not been able to develop in so many ten millions of years a species that would not need to go back to the Sargasso to breed? I am sure you would convince me my question is silly.

DR. MAYR: The question isn't silly at all. Of course, innumerable evolutionary lines, perhaps most of them, become so specialized in certain ways that they get themselves into a dead end and eventually become extinct. That is why the dinosaurs, the pterodactyls and so many other types became extinct.

Eels quite often become "landlocked," that is, they get into lakes from which they can't go back to the ocean, and they become very big. In no single case, as you correctly say, have they been able to reproduce in fresh water by reversing their adaptation of having to go to the deep sea and salt water to reproduce.

This reproductive adaptation of the eels does not depend on one or two genes; it depends on probably hundreds of thousands. It is therefore impossible for a landlocked eel to break out of the straitjacket of its particular genetic program that makes it go back to the ocean to breed. Lampreys, a group of very primitive fishes, however, have succeeded in doing it. Practically all freshwater lamprey species have one branch that goes down to the ocean to spawn, while a sibling species does it right in the freshwater streams.

DR. WALD: The sea lampreys always must spawn in fresh water; they may or may not migrate to sea as adults, but they always spawn and spend their larval period in fresh water, and can remain in fresh water throughout their lives. Conversely, the "freshwater" eels (Anguilla) must spawn and spend their larval lives in the sea, though they have the privilege, not always exercised, of entering fresh water as adults. The proper view is that lampreys—as also salmonids—are freshwater organisms that have the freedom as adults to enter the sea; and the eel is a marine fish with the capacity to enter fresh water. No such euryhaline fish ever *has* to migrate. The mechanism that restricts the fish to one spawning environment is that its sperm, or eggs, or embryos, or all three, won't tolerate the other environment.

As for the survival of such traumatic experiences as metamorphosis and migration, worry about them in the frog, where they are much worse.

I have discussed these matters in a paper called "The Significance of Vertebrate Metamorphosis," (Science, *128,* 1481 (1958) and Circulation, *21,* 916 (1960)).

DR. SCHUTZENBERGER: But how come the selection pressure hasn't the time to play against the one?

DR. MAYR: Neither mutation pressure alone nor selection pressure alone can run evolution. You have to have the proper kind of changes in the genotype so that selection can make use of them.

DR. SCHUTZENBERGER: But you told me that there are species that have been able to dispense with this trip. I would like to know what are the general reasons why what applies at one time doesn't apply at others.

The Chairman, DR. WEISSKOPF: I know that you are an anti-Darwinian and he is a pro-Darwinian, but it seems to me to be clear that the fact that the eel does such a complicated, impractical thing, is to my mind, a very strong argument in favor of Darwin because it shows that nature can work in a very complicated way. It need not do the simplest thing; therefore, it has many more choices. If an eel can survive even with this way of living, it shows that it isn't actually so hard to do it. Therefore, one need not be so surprised that life has evolved.

DR. SCHUTZENBERGER: Then I am surprised that so many species have disappeared.

DR. WALD: I am a little puzzled as to what alternative you are offering.

The Chairman, DR. WEISSKOPF: The eel should have disappeared, he says.

DR. SCHUTZENBERGER: No, I say that I am surprised that such a thing doesn't seem to be so for other species, since they can survive and live in the place where they breed. Why have the eels not been able to develop a mutant type by which they would be able to dispense with a trip which is so dangerous?

DR. MAYR: Maybe they are having a hell of a good time; how do you know?

DR. SCHUTZENBERGER: But then how do you know when it is favorable in the other direction? I just wanted to bring you to this anthropomorphic judgment which you apply one way or the other.

The Chairman, DR. WEISSKOPF: It seems to me that this was a very important remark. Evolution can lead in one case to extinction; in the other, not. I think it was Medawar who said that one thing about the theory of evolution is (and he quoted Popper) that it is not falsifiable, that whatever happens you can always explain it. I think you have an example here.

DR. BARRICELLI: In regard to cultural evolution I would like to point out just one thing, that a language has some similarities to a living species. Languages as well as species evolve by mutation, crossing and selection. A language cannot survive or propagate unless there are humans or whatever species is using the language. But that is a property it has in common with many symbionts and parasites. One may consider a language as a symbiont of *Homo sapiens* of a different nature than the nucleic acid-protein combinations we are used to consider as living organisms.

DR. H. B. D. KETTLEWELL: Dr. Wald, are you admitting that this is symbiosis, your luminous bacteria on the fish, or not?

DR. WALD: Oh, yes.

DR. KETTLEWELL: You hadn't made it clear to me.

DR. WALD: Yes, you are very gently telling me that I had no question, that this is just a rather complicated form of something I should have taken pretty much for granted, and that I am being confused merely by a degree of spatial separation by the symbionts. That is all right, but then this is a symbiosis that involves these mutual adaptations through the whole "eco-system."

DR. MAYR: Dr. Wald, does anybody know whether the fish really derive any advantage from this diffuse bioluminescence? Couldn't it make them more vulnerable to discovery by their predators?

DR. WALD: Yes, but those predators are other fishes. I think that's it. I suspect it is only very, very rarely that bioluminescence is a direct advantage to the luminescent organism, because you mustn't think of this like a flashlight, since it doesn't radiate far. It makes the luminescent organism itself visible to other animals. It doesn't increase that animal's capacity to see other creatures.

There are exceptional cases—that angler fish, for example, which hangs a little light as bait over its great gaping mouth—where being luminous is a direct advantage; but what I have been discussing involves a general mutual exchange of advantages through the whole ecosystem, and that is a little different from symbiosis because it involves so many different kinds of creatures over such a wide range.

DR. FRASER: Do these fish live in schools? This would seem to me to be an important point.

DR. WALD: I think not. The deep organisms, no. That would, of course, make luminescence beautifully useful.

DR. FRASER: Maintaining positions in schools would actually give them an advantage.

DR. WALD: I doubt if anyone knows. The deep sea fish are pretty rare things and I suspect they are more often solitary.

DR. KETTLEWELL: You were asking whether there were inherited characters which might act after childbirth time.

DR. WALD: Right.

DR: KETTLEWELL: I thought of several examples of that. The value of the old, sterile shelducks to the young, which allows

the breeding birds to leave them in the keeping of the "old women." The second one which has been worked out concerns the old, impotent baboons who, like eunuchs, rather, look after the tribe and the younger males eventually do copulate.

DR. WALD: All right, then, your answer would be that one does have selection for these characters?

DR. KETTLEWELL: Absolutely.

DR. MAYR: This is in the literature as sibship selection. There is a great deal in the recent literature.

DR. FRASER: Haldane has given one of them.

DR. MAYR: The question is often asked how one can select for a character that is potentially harmful for its bearer. The answer is that it will be favored by selection if it increases the probability of survival of close relatives (many of them also carriers of this gene) more than the probability of death of the carrier. Let us assume there is a gene for giving a warning call when an individual discovers a dangerous predator. The calling will slightly increase the vulnerability of the caller, but it will facilitate escape by nearby relatives of the caller. Possession of the gene, thus, will increase the fitness of the sibship.

Such a character will become established in a species not because it helps the species as a whole or the population as a whole, but because it helps the sibship, provided this includes other carriers of the appropriate genotype.

This is why the social characters in the bees are so highly developed. They are all members of, biologically speaking, a single family; because the workers, genetically, all belong to the same entity. Darwin pointed this out beautifully in 1859. The workers, whatever they do, benefit other carriers of their genotypes, namely, their queen and her descendants. The principle of "altruistic genes" does not work if it benefits only carriers of different genotypes, because then it wouldn't spread in the population.

DR. COON: A better example than that of the Jesuit, and one which is more in your favor, is a situation in Tibet. There one finds a great deal of monasticism at a high altitude, where the libido of the monks is very low, but when the lamas come down to a lower altitude, their behavior pattern changes drastically.

DR. HOWARD: I want to make a brief comment regarding the possibility that the luminescence from the bacteria on the fish might be deleterious due to predation. We should also remember that predation may be deleterious to the individual but beneficial to the population in its evolvement. It depends on the extent of the predation.

DR. KOZINSKI: To confuse the issue, let me make a statement that predatory fish of the depth are looking *up* for their prey. Small fish which do not produce luminescence form a black silhouette against the faint glow of the surface above. If the fish produces luminescence of the wavelength identical to or close to that of filtered light, it should be less visible or possibly invisible. In this context, luminescence should *not* be a disadvantage but an advantage.

DR. WALD: But there is perpetual night at these depths.

DR. EISELEY: I would like to ask a question, and I do it rather warily, not being an ichthyologist and remembering what happened about the blue green algae. I still would like to ask, in the case of some of these fish that have rows of lights in peculiar patterns along the side or under the eyes, whether there may be a pattern here which is helpful in terms of the individual finding other individuals of its own species, by the pattern? Is this useful in this connection? I wouldn't attempt to explain how this arises but I am under the impression that you do get certain fish with these characteristics.

DR. WALD: In fireflies there is great reason to think that the flashing is a means of bringing the males and females together, to find one another. This could be of great potential use.

DR. MAYR: This is the way in which this patterned bioluminescence is largely explained in the current literature; but let's make a distinction between a fish that has bacteria in its slime and a fish that has definite luminescent organs in which the pattern is species specific. In the deep sea,

individuals of these fish are believed (nobody knows) to be very widely spaced and they have trouble in finding potential mates. So every once in a while each one of them flashes and when they finally find one that has the species specific pattern, they can come together and reproduction can take place. This is the way this is described in the literature.

DR. EISELEY: I am curious about one fish that I do not have the name of but that I can recall reading about, in which apparently the luminescent organisms are under, or in, the eye in such a way that the fish can wink them on or off, although they are separate organisms.

DR. WALD: I have read of such a thing, too, but I don't recall the details.

DR. BRITTEN: I would like to point out one more mechanism which might be involved and that is the distribution of the luminescent bacteria by contact. This would be a rather elementary way of their finding a large area of fertile ground.

Transfer of bacteria might be a rare event except when a predator contacts prey which subsequently escapes. The amount of predation might be greater among species that appear luminescent and thus give the luminescent bacteria an advantage. On the other hand, luminescence might increase the amount of exploratory contact and have little effect on the life of the fish.

DR. WALD: Do you all agree that there is no simple formula for telling a case of cultural transmission from genetic transmission?

The Chairman, DR. WEISSKOPF: I would like to say a word on this. I had always thought that one could make a very simple differentiation between cultural evolution and biological evolution by means of the time scale, but maybe I am wrong. I would like to try it out here. It seems to me that the cultural evolution changes behavior patterns of society in a few generations, whereas biological evolution does so in 10,000 generations.

DR. COON: I would say the cultural tradition may or may not change in a few generations. Sometimes it doesn't change in a tremendous length of time.

The Chairman, DR. WEISSKOPF: Then I would call it biological.

DR. COON: It has the capacity for changing in a few generations.

DR. WALD: My question involves the contribution to natural selection, and I am sympathetic with what you say about this, Dr. Weisskopf, but my question was really in terms of effective mechanism of selection. Granted that there is such a difference in time scale as you describe, is this a parallel way to achieve selection?

DR. WADDINGTON: Surely this has to be resolved experimentally. If you want to know whether a bird's song is transmitted through its genes or through its parents, you take the eggs away, incubate them artificially, and see how it sings. In some cases you do find it sings a perfectly good bird song, a species specific song, without ever having met a member of its species before; so it can't be social. In some cases you find it doesn't. This is perfectly determinable experimentally.

The Chairman, DR. WEISSKOPF: But I think the problem is a slightly different one, because here I agree with Dr. Wald. I believe that in the animal kingdom there are many cases in which there is transmission of certain behavior patterns by teaching or by imitation, or whatever you call it. But the point is, to my mind, whether the occasion of doing so, the urge of doing so, is inbred in the biological index or not. This, it seems to me, is indicated by the tempo of change. The bees have their dances, and so on, for many, many generations. The same is true for the learning of songs by birds, whereas the behavioral pattern in man changes within a few generations. It is not, therefore, biologically determined.

DR. WALD: There is often an intimate relationship between these two factors—nature and nurture. In man, for example, you have an enormous overprojection on the brain of the areas connected with the hand and the mouth. You also have the cultural transmission of hand skills and speech, both of which have to be learned, but which have already had provided for them this anatomical substrate. The thing that interests me most here is the question,

is cultural transmission alone agreed to be a very effective way of achieving a certain kind of inheritance, which, until one does these experiments that Waddington talks about, is indistinguishable from genetic inheritance in its evolutionary effects?

DR. FRASER: It would seem to me that there have been endless statements made and the only thing I have clearly agreed with through the whole day has been the statement made by Carl Popper, namely, that the real inadequacy of evolution, esthetically and scientifically, is that you can explain anything you want by changing your variables around. There is a real value in the statement, "It is not worth discussing this because a single experiment will decide the issue."

DR. WALD: The experiment is fine, once it has been performed. It usually hasn't, and the fact that when it hasn't we frequently cannot decide which is which seems to me strong evidence that in natural selection cultural inheritance plays an analogous role to genetic inheritance.

DR. FENTRESS: I think we can carry Professor Waddington's comments a little bit further. The main point is that you have to ask a much more limited question. For example, we take our bird and we raise this bird in isolation and we find that species A does now give a song which is indistinguishable from the bird in its normal environment. We cannot, however, say that experience in this bird is not important for developing song.

For example, you can do the next experiment in which you deafen the bird. In other words, it then has no auditory feedback; and in certain cases you find, sure enough, the bird now cannot develop a song.

So, instead of asking the question, is this song innate or is this song learned, you can simply say that you do an experiment, you manipulate a particular variable, and this variable does or does not have an effect upon the song.

The complex interactions possible between genetic potential and environmental factors make precise estimates of stored information difficult. This is a problem we have discussed much in the present conference. Thus, if auditory feedback can provide some information leading to the development of a normal song, the information load on the genes can be reduced. This may lead to considerable economy. Many other processes may also contribute to the total information available at various stages of development.

DR. BARRICELLI: I would say that the cultural patterns are in a sense a solution of the problem of having a form of inheritance which doesn't require killing of individuals in order to evolve. You can evolve them by selecting for cultural patterns, and in this respect it would be a much faster evolutionary phenomenon. This would apply to civilization in general.

On the other hand, when we compare them with biological phenomena, I would say cultural patterns cannot always be considered as an inheritance of the single individual; some of them may be an inheritance of the culture as a whole, comparable in some respects to symbiotic entities, which can be communicated from human to human or from population to population and in this way can reproduce. Cultural patterns can therefore be symbionts either of the human population or of the individual. If you take an individual alone, reproducing on an island for himself, he may invent his own language but he won't learn the language of the community. So a language or a cultural pattern has something in common with an infection acquired by contact with an infected population, what we call a parasite or a symbiont or whatever you like.

DR. EISELEY: I would like to venture just one comment on this whole problem of culture. A few days ago I happened to sit in a conference in which a well-known anthropologist made the statement, in connection with what was being discussed, that there were no genes for criminality, that every criminal was the product of society.

Now, this statement can be misinterpreted. There is not a gene, let us say, for a specific crime, as bank robbing or forgery. On the other hand, I think that there is a range of human temperament that is in

some degree genetically controlled. I think the mass of individuals runs through a wide spectrum in this connection, and that there are certain individuals who may be more susceptible as a consequence to a criminal response in the proper environment. This may be true of any number of other cultural activities. Such persons may be, by genetic chance, more adept at them; I don't care whether it is some form of athletics, for example, that they happen to be gifted for, or some type of intellectual activity. But as has been remarked, a given culture can intensify or to a degree select for social approval if it is long sustained. The type of temperament which is allowed expression in certain formal ways can be selected. There may be other things within the confines of a particular culture which, on the other hand, by chance may be suppressed to the degree that those individuals, or individuals having some genetic bent in a particular direction, are actually discouraged; or the opportunity for them to distribute their genes in that society, if it persists long enough, may be reduced. So I think there is an intricate interplay here between the cultural and biological which is very difficult to separate successfully.

The Chairman, DR. WEISSKOPF: Dr. Eiseley, now really, you are speaking of something completely different; because it seems to me this question would have something to do with what we are talking about, only if the criminals would get more children than the good people.

DR. EISELEY: This is quite true and I don't wish to argue this at all. This particular remark, let me say I regard as extreme in this connection.

DR. WALD: I think Dr. Weisskopf is assuming too much here. I don't think that is true. I think we would all grant that all aspects of the behavior of worker bees, including all aspects of their behavior that they learn, react upon the selective advantages and disadvantages exhibited by that hive, whether the behavior is innate or learned. We are in the same boat. As Darwin pointed out in the "Descent of Man," the competition for survival among human societies depends upon cultural factors—ethics, esthetics, mores—just as on innate biological factors. Incidentally, we tend to take it for granted that all bee behavior is genetically determined, whereas we tend to assume, unless there is elaborate proof to the contrary, that human behavior is culturally determined. But in the human case there is no doubt that in the competition for survival of nations and societies, cultural factors are of the highest importance.

The Chairman, DR. WEISSKOPF: I think perhaps I am taking advantage of my role as Chairman, but let me say that as long as it doesn't have an effect on the number of births,—

DR. WALD: It does!

DR. WEISSKOPF: This depends on the amount of birth control practiced by criminals.

DR. WALD: That raises another question —whether fitness is simply to be measured by number of births, which I doubt very much.

DR. WADDINGTON: Can't we simplify the situation by leaving man out of it? It is clear that behavior, animal behavior in general, is one of the things that determines the type of selection pressure that is going to operate on the animal. According to where and how it lives, it will be submitting itself to different environmental stresses and selection pressures. In a great many animals, behavior patterns are very largely innate, and it is very difficult to teach them to change these patterns and thus alter the selection pressures; but in certain animals, like birds, they can do so rather well. There is one nice example of a change in a behavior pattern transmitted almost certainly by social teaching, which has affected selection pressures on birds. Blue tits in England have learned to take the tops off of milk bottles and to drink the cream. This habit spread over Europe; I think it spread from three or four different centers, one of which was in England. It spread within a few generations, much too fast to have gone by genes. This was almost certainly transmitted by some system of imitative learning, and of course it brings in a new source of food supply, thereby changing the whole ecological setup of selection pressures.

One can imagine that later on these tits might develop a changed articulation of a thumb which would enable them to balance on the rim of a milk bottle while they are drinking, or something of that sort. But this is a nice example of a socially transmitted behavior pattern affecting selection.

DR. SHAHN: Without affecting the number of births?

DR. WADDINGTON: No, this is a form of earning a living.

DR. LEVINS: I would like to express perhaps a minority view here, differing with Popper on the question of falsifiability in the interpretation of evolutionary theory. I think the model of a laboratory experiment, the critical experiment of physics, is not an adequate one for the macrotype theories that we are concerned with here any more than, for instance, the hypothesis that the differential operator is a useful description of nature is a falsifiable one. You get differential equations that work and also lousy ones which don't tell you anything, but which do not cause us to reject the calculus.

What evolutionary theory does here is not explain everything but suggest how to find out. In relation to the eel, Darwinian evolution would suggest certain kinds of critical experiments. For example, one possibility is that the developmental system of the eel requires two kinds of environments at present and, therefore, it cannot complete its development without being exposed both to fresh water and salt water.

A second alternative is that, in fact, natural selection is maintaining it in this behavior pattern in spite of the cost of migration, because that way it may be spreading its competition over several competitors instead of having all its competition concentrated with one.

This would suggest possibilities, for example, that if the eel refuses to mate in fresh water, we could do experiments of artificial breeding to see whether the eggs are viable in fresh water, even if they wouldn't naturally lay them there; and using some of the more sophisticated techniques of the Baldwin effect, we could see if we can change the selective circumstances so as to change the biology of the eel. Therefore, the evolutionary theory suggests experiments while it, itself, is not being tested.

DR. WALD: May I ask a question about a third possibility? Incidentally, may I say that the strange thing in the behavior of the eel is not that it goes to the Sargasso Sea to spawn; it sort of belongs in the Sargasso Sea. The strange thing is that it comes up into fresh water as an adult, which it does not have to do, not at all. The eels can stay in the ocean all their lives and go through a perfectly normal life cycle there. It is that coming into fresh water that is queer.

Now I want to ask my question: How about the third possibility? Does the explanation for the strange behavior lie in the previous history of eels?

DR. LEVINS: Previous history only operates through present circumstances, either as a history of a developmental system which doesn't allow modification, or as a previous system of selection such that its present ecology doesn't permit modification.

DR. MAYR: I think here we need to say something on the natural history of the eel. First of all, there is a Pacific eel that does the same thing; it goes off to the seas south of Sumatra, spawns there, and the immature return to fresh water. Secondly, the oceans are full of eels. All the others are salt water eels and do not have part of their life cycle in fresh water; so this originated by one species discovering, in its juvenile or semi-adult state, a new expansion of its food niche, which it has successfully utilized. However, its whole reproductive system and embryology is adapted to salt water spawning, hence the return migration.

DR. CROSBY: Just going back to the question of blue tits and eels, the question, in fact, is really more complex; because the blue tit is not the only species that has discovered how to take the tops off milk bottles. This raises the problem as to whether the other species, the great tit is one and I think the chaffinch, have discovered the habit anew, or whether, in fact, a cultural habit developed by the blue tit has been transmitted or learned from the blue tit by the other species?

DR. WADDINGTON: If birds can learn songs from each other, why shouldn't they learn this?

DR. KETTLEWELL: How be it, then, if birds work by copy, that the British blackbird starves in drought because it can't hammer a snail on a rock but a thrush survives because it does this on its anvil so successfully? The blackbird will then come and take it when the snail has been smashed. Why has the blackbird not learned this, if they are so good at copying?

DR. CROSBY: Perhaps the blackbird is one species that isn't copying.

The Chairman, DR. WEISSKOPF: Perhaps the most incredible question is, how the eel finds his way to the fresh water?

DR. SCHUTZENBERGER: I'm sorry, there are several discussions which are going on at the same time. Dr. Levins, I don't think I understand exactly what you said. There is no theory of differential operator applying to physics. There is mathematics, in which the theory of differential operators is a chapter. Second, there is physics, which is concerned with what sort of differential operator can apply on this and that occasion. One could make the claim that the main task of physics is to describe when something will work and when it will not work. Here, in the case of eels, it seems to me that the only thing you have stated is that it doesn't work because it doesn't work. This is very different from physics.

DR. WADDINGTON: Could I compare it to cosmology? What you are really asking us to do, in asking us to provide a theory of evolution, is to explain the existence of a particular species, such as an eel, which has a funny behavior.

If I asked the physicists to explain the fact that there is a cluster of stars in the sky looking like Orion, which is a very funny thing to discover, you would have to give exactly the same kind of answer as we are giving about biology. Your physical theories would be unfalsifiable in exactly the same way. If there wasn't a cluster of stars in the skies looking like Orion, but it looked like Andromeda or some other mythological figure, your theories would be just as good for Andromeda as it would be for Orion; and our theories of evolution are just of this kind.

DR. SCHUTZENBERGER: I wish to answer because it is not the point of astronomy to explain the shape of constellations, but if astronomy had only to say that three stars make a triangle whenever they make a triangle and that they don't make a triangle whenever they don't make a triangle, the whole theory would be rather empty.

A science consists also of a selection of questions or problems and of a general framework within which it can be decided if a question has been answered or not.

Now, we are very happy that fireflies meet each other by making light. I am sure they have an extreme pleasure in that; but it would be interesting to know why only the fireflies do it? Is there any general reason which could be given for them inventing the idea of light? Why does this species need such a complicated mechanism for mating when anybody does otherwise?

For any specific question you can provide me with a specific answer, but I would claim that in most of the circumstances there was no general principle on which you could decide in advance which type of specific explanation you would use for it. I think this is exactly what it means to be a nonfalsifiable theory.

DR. WALD: I would like to speak to that for just a moment. I think that you are tending to mix up some things which are clear and some things which are more obscure. Perhaps I could help out a little bit by saying that the fireflies, for example, give me no trouble. Bioluminescence is a possibility and they seem to be using this, but the question, "Why not all flies?" is not an allowable question. Various organisms try various things; they keep what works and they discard the rest.

But let me say as a fellow biologist, (though not nearly the biologist that Ernst Mayr is), that I find his discussion of these eel migrations completely unacceptable. They just don't ring true to me. That is, the thought, "Ah, yes, you see those eels have an adaptation such that they can only spawn in the depths of the Sargasso Sea; and these other eels have some other adapta-

tion that makes them spawn in fresh water." Incidentally, just as our eels are coming up into fresh water to grow, there is a large variety of other fishes that happen at that moment to be going down to the sea for the same purpose. Then as the eels start back to sea to spawn, those other fishes are coming upstream to spawn; so they are going in opposite directions.

It doesn't help me with this to announce that whatever you find organisms doing is an adaptation. I am very skeptical of that. I think, on the contrary, organisms may continue to do those things that they are not forced to stop doing. I would much rather believe that the Sargasso Sea is the place of origin of those eels; somehow or other they have developed a habit which persists in this situation. I think there should be a little evidence, or at least it should be made a little more plausible, why it is true for eels that they cannot in fact carry out their embryology in fresh water. But such evidence would only tell us why they need to take a very short trip, just the trip out of fresh water into salt water, not the 3,000-mile migration that they do make.

DR. EDEN: I would like here to come to the defense of Dr. Popper. I think we should make a clear distinction between falsifiability and use. I am not denying and I don't know that anybody else is denying the usefulness of evolutionary concepts as means for looking at problems; but it is a theory of a different kind. We may contrast it with theories of physics. Certainly Newtonian physics is falsifiable. Even in biology, I recall one occasion on which I helped develop a very ingenious and very plausible theory regarding the countercurrent mechanism in the kidney. It was not only falsifiable, it was false. My point is that for such a theory one could propose a crucial experiment and check as to whether or not the theory was false or not.

This cannot be done in evolution, taking it in its broad sense, and this is really all I meant when I called it tautologous in the first place. It can, indeed, explain anything. You may be ingenious or not in proposing a mechanism which looks plausible to human beings and mechanisms which are consistent with other mechanisms which you have discovered, but it is still an unfalsifiable theory.

DR. FENTRESS: I would simply like to give one example which I think illustrates how important it is to ask a precise question. When I was in Cambridge, we were working with two species of British vole.

We had a little test in which an object moved overhead; one species would run away and the other species would freeze. Also, one species happened to live in the woods and the other happened to live in the field. This was rather fun, and, not really being a zoologist, I went up to see some of my zoologist friends and I reversed the data. I asked them, simply, why a species which lived in the field should freeze and why one that lived in the woods should run away (when the converse was the case). I wish I had recorded their explanations, because they were very impressive indeed.

Algorithms and the Neo-Darwinian Theory of Evolution

DR. MARCEL P. SCHÜTZENBERGER
University of Paris, France

DR. MARCEL SCHUTZENBERGER: Our thesis is that neo-Darwinism cannot explain the main phenomena of evolution on the basis of standard physico-chemistry. Here we stress two points. First that the physical concepts used by biologists are generally more classical (or less imaginative) than the ones occurring in such domains as, say, cosmology. Second that we are not trying to smuggle in extra scientific principles. Thus if we claim that radically new principles are needed we also believe that these have to be found within physics. The nature of the inability of biology to provide a coherent explanation of evolution is best seen when contrasting it with geology. It is certain that no one can work out mathematically every detail of the geological history of the earth. However, for each of the most important phenomena, there exists a simplified model which accounts for it, without mysterious forces, and there is no doubt that this chain of models could be refined *ad infinitum* without gaps and without requiring the verbal argument so often met here that new qualitative effects arise because of the enormous number of small quantitative variations. At no point does geology need to use such phrases as "creation of information", "increase of efficiency", "self-organization", and the like. (My examples are chosen so as to offend no one here, I hope). I intend to restrict my argument to show the existence of a serious gap in the current theory of evolution. The next question (which I will not discuss here) would be to ask how much random mutation and selection would be needed once this gap is filled.

My colleagues this morning have been doing their share of sand reckoning in the manner of Archimedes. From their talks it is clear that even on the most schematic models the number of cycles involved is truly enormous. Thus, when we reach the level of 10^{1000}, whether or not we take a few square roots makes little difference in this cosmos. A second point to which I would like to draw your attention is the fact that nowadays computers are operating within a range which is not entirely incommensurate with that dealt with in actual evolution theories. If a species breeds once a year, the number of cycles in a million years is about the same as that which one would obtain in a ten day computation which iterates a program whose duration is a hundredth of a second. Our ability to play with iteration of this magnitude is quite a new thing, and we can begin to develop some concrete experience with this type of process. It was not so in the time of Fisher and *mon bon Maître* Haldane, and now we have less excuse for explaining away difficulties by invoking the unobservable effect of astronomical numbers of small variations.

To present my argument I need to introduce a schematization of current ideas based on the introduction of three spaces, each endowed with a specific net of proximity relations, or as I shall say for short, a topology—if you forgive my using mathematical jargon.

According to the "dogma" of molecular biology the first level we start with is, ideally, something like a big book written in an alphabet of 20 odd letters. This is the blueprint of an individual, a genotype. Further we have a genic pool, i.e., a collection of such books which are variants of each other. For many clusters of species this collection is not much bigger than the Widener Library; for others, it is at most millions or billions of times larger. I shall

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take those books as the elements of the first space, and, since we are not in any way Lamarckian, we have to admit that the proximity relations in this space are of a strictly typographic nature: omission, addition, duplication, transposition, or change of letters, pages, or of chapters—but irrespective of context, or if you allow me, of meaning. This topology, insofar as molecular biology is concerned, is of the same nature as the one which would represent the relations between several copies of the same manuscript typed and bound by a very careful assistant totally ignorant of the language in which it was written. Typically, in the typographic topology, two editions of the same textbook of botany differing only in the fact that one contains the common name of species wherever the other has the Latin name, would be further apart than two editions differing by replacement (or deletion, or duplication . . . etc . . .) by another word or jumble of letters perpetrated in a systematically random manner, of one or two words in each page.

At the opposite end we have the individuals who react to the environment in accordance with their being physico-chemical systems with a given size and configuration. Admittedly, it may be hard to give an abstract formulation of the fact that two trees (or two winged animals, or two protozoa) are "closer" to each other in the topology of phenotypes than are, say, a bush and a bird. However, this system of closeness relations is the one on which we base most of our taxonomy and physiology. It is with reference to this topology that one tries to account for the similarity of the selective effects of the milieu when discussing phenomena of convergence.

In the middle, neo-Darwinism introduces a third space consisting of vectors (i.e. finite sets of numerical parameters) with its usual topology. The coordinates of these vectors are such things as mutation rates, coefficients of viability, etc. Because this is a theoretical object, it is not dramatically surprising that one can predict or simulate Darwinian effects within it. One might question the adequacy of using the parameter space as a model for the phenotypic space and the validity of the reasonings based on it because in almost every case, both the parameters and the relations between them are strictly hypothetical constructs for which no conceivable direct or indirect cross measure exists. We shall not do it here because we believe that the crucial difficulty is not in relating this theoretical parameter space to the real phenotypic space but in providing a link, however tenuous, between either of them and the space of the chains of amino acids (or the space of genic pools, it does not make much difference) endowed with its specific typographic topology.

Indeed, what we have at each of the two extremes is not even chaos out of which one might believe that a certain regularity could emerge, as it may do in thermodynamic processes, but two systems having structures (topologies) which *a priori* are not more in agreement than in conflict. Now some modicum of agreement is needed if one wants the selection pressure to have the nice effects we are told it has. Otherwise, there is no reasonable probability (say more than 10^{-1000}) that variations in the milieu operate without the genotype having entered a *cul-de-sac* out of which no evolution is possible.

I apologize for being so assertive but here is the point where experience with computers (more seriously, of course, a few mathematical results) comes in. According to molecular biology, we have a space of objects (genotypes) endowed with nothing more than typographic topology. These objects correspond (by individual development) with the members of a second space having another topology (that of concrete physico-chemical systems in the real world). Neo-Darwinism asserts that it is conceivable that without anything further, selection based upon the structure of the second space brings a statistically adapted drift when random changes are performed in the first space in accordance with its own structure.

We believe that it is not conceivable. In fact if we try to simulate such a situation by making changes randomly at the typographic level (by letters or by blocks, the size of the unit does not really matter), on computer programs we find that we have no chance (i.e. less than $1/10^{1000}$) even to see

what the modified program would compute: it just jams. We can specify what it would take to have the random modifications introduced so that a sizable fraction of all programs start working: It is a self-correcting mechanism which must incorporate something like a symbolic formulation of what "computing" means. Thus no selection effected on the final output (if any!) would induce a drift, however slow, of the system toward the production of this mechanism if it were not already present in some form. Further, there is no chance ($<10^{-1000}$) to see this mechanism appear spontaneously and, if it did, even less for it to remain. Finally, we can predict what would happen if such a mechanism had been installed: for almost all the mutations the computation performed would have no relationship to the ones executed before; hence, no relationship to the selective pressure exercized on the output. All this, I repeat, is a simple consequence of the lack of matching between the space of the outputs and the space of the programs. This, of course, does not apply to the relationship between the space of parameters and adequate simplified models of the space of genotypes: They are theoretical constructs which have been specifically designed to fit. However, the question remains with respect to the relationships between the space of the chains of amino acids and the space of the organisms (or just as much, the parameter space studied by Sewall Wright). We do not know any general principle which would explain how to match blueprints viewed as typographic objects and the things they are supposed to control. The only example we have of such a situation (apart from the evolution of life itself) is the attempt to build self-adapting programs by workers in the field of artificial intelligence. Their experience is quite conclusive to most of the observers: without some built-in matching, nothing interesting can occur.

Thus, to conclude, we believe that there is a considerable gap in the neo-Darwinian theory of evolution, and we believe this gap to be of such a nature that it cannot be bridged within the current conception of biology.

Discussion

PAPER BY DR. SCHÜTZENBERGER

DR. ULAM: My impression is that what you have said so far is that one does not understand now how the blueprint determines the existing physical objects. That, of course, the Darwinians or neo-Darwinians would readily admit. Now, the assertion that such blueprints exist and are important is made much clearer through the discovery of the genetic chains as codes. Nobody in the 19th century or even now would profess to understand the details of how, from the code, an actual organism is produced.

DR. SCHUTZENBERGER: We are not worried with the details. The only thing is that I would need an example where such a correspondence would exist or could exist, even in the simpler case.

The Chairman, DR. WADDINGTON: You have confronted us again, you have made the gap because you have left out the middle space, the epigenetic space.

DR. WALD: What is epigenetics? What does the word mean?

The Chairman, DR. WADDINGTON: It is a derivative of an old Aristotelian word and means the study of the causal mechanisms of development. "Epigenesis" was used by Aristotle to mean that new things appear during development. Epigenetics is the name for the study of the causal interactions between the genes in the blueprint and the way they work together to produce first proteins, and then cells and membranes, myosin fibrils and God knows what. It is the causal study of the way the genotype space is translated into the phenotype and if you leave it out, of course there is a gap. Unfortunately, however, we can't yet put it

on computers! We really have got no analog of development. This is why the whole application of information theory to biology breaks down; because what biological organisms do is to treat information as axioms and then develop theorems from them, and this is something which isn't included in information theory, as it is normally understood. Information theory is a conservative theory, in which information can't be increased. But biology, as it were, starts with Euclidian axioms and proceeds to write a five-volume treatise on Euclidian geometry, and it is that process which goes on in this middle space of epigenetics and leads you into the space of phenotypes. But nobody has yet found how to do it on computers and therefore, it tends to get left out.

DR. SCHUTZENBERGER: I repeat, in order to mediate between the space of chains of amino acids and the real world of organisms, some new construct has to be introduced, and principles have to be stated explicitly explaining how this mediation is conceivable.

At the level of molecular biology, we are told that we have a reasonably complete description of the mechanisms. Also, physiology is providing us with an understanding of organs. However, everybody seems to take for granted that there is no gap in between. I am not discussing the adequacy of each of the two extremes. I just point out that nobody seems to be able to give reasons why they have anything to do with each other. If there were explicit general principles relating them, then we should be able to simulate something analogous, and we would have a lot of fun studying mathematical models showing the passage from disorder to order.

DR. ULAM: What you are saying, it seems to me, is that the Darwinian and neo-Darwinian theories are not complete, and everybody agrees with that; but it is not an objection to the scheme of things, which is sort of lost sight of.

DR. RICHARD C. LEWONTIN: Can we give you a practical experience where there is no gap? Will that suffice? Suppose I tell you that I know exactly the typographical change involved in a mutation of the enzyme tryptophane synthetase. I know what that change is and I know many such changes cause an inactive enzyme to be formed.

I know that an organism which is not fed tryptophane, if it is an organism that requires tryptophane in its proteins, will not succeed in dividing and reproducing if it has that typographic change. Therefore, the frequency of such organisms will decrease in the population and be replaced by those that can synthesize tryptophane.

Excuse me, but what step is missing in this argument?

DR. SCHUTZENBERGER: It is missing the decisive step. Maybe I have too ambitious a goal with respect to evolution theory; but it seems to me that if its principles were valid, we should then obtain on simplified models the same type of correlation which you claim to obtain. However, what we know is that when we make changes of a typographic nature, most of them are meaningless from any respect, and when I say "most of them," I mean less than one out of 10^{100}.

DR. LEWONTIN: No, that is not true.

DR. ULAM: Tell him, Dr. Schutzenberger, *where* his model fails.

DR. LERNER: Would you answer Dr. Lewontin's question?

DR. SCHUTZENBERGER: It is very intriguing, but if you tell me that the coding is such that this type of change induces meaningful changes—what I mean by "meaningful" is that they are related in one way or another to external individual characteristics—you already express a very strong hypothesis on the living system. I say this is not included in molecular biology as it is described now.

DR. LEWONTIN: If the speaker objects to a case in which the enzyme has been destroyed in its action, then I can give him known cases where the enzyme, far from being destroyed, is changed in its pH optimum, changed in its isoelectric points, changed in a number of aspects of its physiological function by single substitutions of single amino acids. We know exactly where in the phenotypic topology of the protein these amino acids have been substituted, and we can specify exactly in what way they change the physiology of the organism, changing its fitness in the write-in space.

If you want, I can give you reference after reference.

DR. SCHUTZENBERGER: Yes, I can also give you references.

DR. LEWONTIN: As in hemoglobin.

DR. SCHUTZENBERGER: I can also give you a lot of anecdotes on typographic changes of books which transform some perfectly decent sentences into ones which are very funny to read in French.

DR. LEWONTIN: But, sir, I have said that they are not meaningless changes; they are changes that change the organism in its phenotypic optimum from one set of environments to another one.

DR. WEISSKOPF: I think the point Dr. Schutzenberger makes is the following: Dr. Lewontin is talking about changes in the enzyme by faults of reproduction; but Dr. Schutzenberger says that this is only a very, very small part of the typographic space and most of the changes seem to take place somewhere else in this space.

DR. SCHUTZENBERGER: I want to say that it is an observed fact that life works.

DR. WEISSKOPF: No, no, let's speak to the tryptophane!

DR. SCHUTZENBERGER: I want to know how I can build, on computers, programs in which —

The Chairman, DR. WADDINGTON: We are not interested in your computers!

DR. SCHUTZENBERGER: I am!

DR. BOSSERT: Perhaps I misunderstood, but I thought yesterday there was some discussion about a point quite in line with what you are saying. You have mentioned variation several times, and you require that a small variation at one level translate into a small, meaningful variation at the other. In fact, I think it came up several times yesterday that those instances where a small variation in the program space translates into a large variation in the phenotype space or output space, are usually of no interest.

DR. SHAHN: My understanding is that the problem involved is how you get from a lower organism to a higher organism; or at a different level, perhaps, what is it about the genetic material which is going to differentiate a horse from a pig; not how one bacterial strain will die due to the deficiency of one enzyme.

However, the argument as it is presented, I think, could probably be leveled against all of biology in that, insofar as I know, there is not one mechanism which is completely understood. Any time there is a difficulty in getting from one step to another, an enzyme is introduced which often can be isolated, its properties in many ways expounded; but the mechanism is still left in a "black box". Using this terminology, one might be tempted to say that organisms have built in a "selectase," perhaps a "fitnessase," and these are part of an operon which is governed by "evolutionase." This now reduces all of evolution to the same state that most of molecular biology has been reduced to, and since molecular biology is today fashionable, I might claim to have solved all of evolution at the same level. I just have to isolate the enzymes.

DR. SCHUTZENBERGER: I want to make clear that my point is methodological, strictly methodological, and now we are just discussing facts. I am asking the question, How can you devise a program (or a book) such that typographic changes are meaningful? You are not interested in computers; I'm sorry. I am not very much interested in computers either, but here is an instance of a problem of order-disorder, and I am speaking of computers just to follow the *Zeit-Geist.*

How come that a system, which is not the type of system imbedded in the usual space-time topology, has the property that small changes within this typographic topology are meaningful? I could be specific here; I could document it with theorems.

DR. LEWONTIN: I gave you an example.

DR. SCHUTZENBERGER: I am not asking for examples. I believe you! But, I say, How come these changes are meaningful?

The Chairman, DR. WADDINGTON: He asked a methodological question. You have to answer it as a methodological question. He has asked, How do you arrange that typographical errors, changing letters and so on, have meaning when translated into this space? Surely, the way you do it is to have the typographic script set up as paragraphs with logical structure in the para-

graph. Most typographical errors will then be absorbed by the logic. You will see that there is a misprint and go on reading, understanding perfectly well what is happening. Occasionally, a misprint will change a key word into some other key word, and actually change the logical structure, but very rarely.

The main point is that your typographic space contains meaningful blocks. It is not a set of isolated individual words. It has meaningful blocks of connected connotations and this can absorb a great deal of typographical error but can occasionally have its meaning changed.

The very simplest case is where the epigenetic space is very reduced and you are just producing an enzyme; Dick Lewontin has pointed this out. In more complicated cases, like the mouse, where the development from the genes to a front leg is much more complicated, you have much longer blocks.

DR. SCHUTZENBERGER: I am sorry, I want to challenge you somewhat. I am sorry to disagree flatly with the Chair. This is not an explanation but a postulate.

When you have said that there are meaningful paragraphs, you have already postulated the simplest thing, which is to make a computer program work at the paragraph level. For the time being there is no such possibility except by introducing beforehand the concept of meaning into it. There is dramatic change at the algorithmic level (that is the first time I have used the word but let it come now) between typographic errors of any sort and the ones which would preserve meaning. Taking paragraphs instead of letters is immaterial; it makes the case worse, that is all. So, what you say is all right except that what you propose is exactly the mechanism for which I am asking.

DR. BARRICELLI: The speakers seemed to stress very much the point that every step from one genetic pattern to another should be meaningful, but I think there is absolutely no requirement that every step should be meaningful. First, you have many examples of changes indicating that often a large part of a protein molecule can be unimportant or play no role in its function. You can lose a piece, you can add a piece, you can shift the reading frame in a segment of the RNA-molecule coding for the proteins, and so forth, and still leave the wild type function intact. That is one part of it.

Secondly, everybody can tell that by typographic change of the various types which have been mentioned today, you can change "Hamlet" of Shakespeare into Dante's "Divine Comedy," just by adding and subtracting pieces and changing one letter to another. So, if you don't require that every step in every place should be meaningful, you can make any large change you want.

DR. SCHUTZENBERGER: I think there are two points here. First, it seems to me that this reckoning activity has some merit in that it shows that the matter is not that all changes must be meaningful. Only a reasonable proportion has to be. By "reasonable proportion," I would mean $1/10^{100}$. It is not the case. We have a conflicting experience. You can quote me experiences where things work in life, but we have a conflicting experience in the computer. Although our processes are based on the same principles as the ones you state explicitly and the probability of a meaningful change is not one in 10^{100}, it is entirely negligible.

The second point has no relationship to the present discussion, but it has a more general bearing on these two days' discussion. It seems to me that it is a nice intellectual game to try to find that there is some path from A to B, but the problem is not to discover *if* there is at least one path. The problem is to decide if there is any reasonable chance of *finding* such a path; it is an entirely different question.

DR. LEWONTIN: I think I understand finally what Dr. Schutzenberger is getting at, and that is that the difficulty (and I agree entirely) is that most of the changes in a given environment would seem to alter the function in a way which is not, as you put it, meaningful. I think the thing that has been left out is the fact that we agree with this point, and it certainly is true, but that in a new environment the old messages, which had meaning in the old environment, now can no longer be called "correct" and changes can no longer be called "errors." On the contrary, as environment changes,

the present messages are no longer in a meaningful language and, therefore, new changes that occur are more likely to produce a real meaning in the new context.

That is the one point which I think all evolutionists are agreed upon, that it is virtually impossible to do a better job than an organism is doing in its given environment.

DR. SCHUTZENBERGER: I suppose we are getting nearer to an exchange of messages, but I was making a stronger point. When I said "meaningful," I was meaning meaningful in sort of an absolute sense. I say that all systems, similar systems that I know about, become meaningless in a radical fashion, when I make these sorts of changes.

DR. WEISSKOPF: In any environment?

DR. SCHUTZENBERGER: Yes, in any environment.

The Chairman, DR. WADDINGTON: This is not the case with the biological aspects.

DR. SCHUTZENBERGER: O.K. I have also the idea that something more must exist in biological systems, but the problem is to find the recipe so that we can simulate it on a different material.

DR. LEWONTIN: I think the answer is that you have over-estimated the number of absolutely meaningless changes that occur when you change a single nucleotide. If we list all single nucleotide changes and the known translation vocabulary between nucleotide triplets and insertion of amino acids, and then we list for a given protein all the results on that protein of changing amino acids all over the molecule, we will find, in fact, that a very large proportion of those do not render the molecule meaningless in an absolute context.

DR. SCHUTZENBERGER: You tell me it is factually all right. I ask you, What is the mechanism which makes it so, or what sort of conceptual mechanism could make it so? I don't know of any general principle or of any trick which in any other circumstances could produce this effect.

The Chairman, DR. WADDINGTON: Before we go any further, I think that, first of all, we should agree how we are using the word "meaningful." I think Schutzenberger means that when he changes something in program space, nothing comes out at all.

DR. SCHUTZENBERGER: It doesn't give support to any epigenetic effects.

The Chairman, DR. WADDINGTON: But actually when we change something, *some* protein does come out; it may not be a very good protein, but some protein comes out. All proteins do something, so all changes in the program level have meaning, in the sense that they produce a protein, except for some full stop marks, and so on.

DR. MAYR: Are you basically asking, why do molecules have such-and-such properties? Why are molecules the way they are? Is that really, basically, what you are asking?

DR. SCHUTZENBERGER: That's a good question. I don't think I have time to answer it now.

DR. LEVINS: I think the missing ingredient in this analysis is that you have left out evolution. The error of the reductionist methodology is to start out with a lower level and attempt to derive a higher level from it without considering the reciprocal relation. In fact, its topology is, itself, a product of evolution and we can start out with a given topology and describe how natural selection will modify this without knowing about the original underpinnings, especially as you get further and further away from the site of gene action to the interactions of these gene products. This is something which, in your library, would have to be described by 10^{10} simultaneous partial differential equations.

On an evolutionary level, in terms of some epigenetic parameters involving elasticity, the rigidness of the terrain and other things can tell us how the evolution is going to change it, the direction of homeostasis, of epistatic interactions, so that, in fact, the topology is the result of evolution.

DR. SCHUTZENBERGER: O.K., This is far easier to answer. You are falling into what I might call the Ashby trap. You only make the case worse by supposing that the mechanism which induces an agreement between the topologies has been produced also by random changes. That is to say, this sort of fallacy has been used a lot of times in "artificial intelligence" to pretend that one could write programs by machines which would learn how to tell themselves how to improve programs.

Still, then, at this level, the probability of meaningfulness is still slimmer by orders of magnitude which are 10^{100}.

If I had had more time, I could have dissected the typographic changes into three levels, each corresponding to a type of algorithm; each of them is practically irreducible to the previous one.

The Chairman, DR. WADDINGTON: Your argument is simply that life must have come about by special creation.

DR. SCHUTZENBERGER: No!

VOICES: No!

DR. FRASER: Can I contrast one computer with another? You have a computer programmed to examine the statement, "All I am allowed to do is change letters and I hope I produce a program. Any kind of program will do." This doesn't work. We now turn around and set up another computer, and we tell it a basic genetic system of plus-minus alleles in which we are saying, "Can it produce information?" The decision on whether the information is useful will be a selective one of "survive or not survive." This is the same kind of decision-making; the programs look very similar to those which are being constructed to try to produce information-containing programs. The principles are very similar.

However, in the genetic one, the system is that there are multiplicities of pathways to suitable answers. The machine can gradually, step by step, get there; each step takes it toward the answers, and it produces them when all we have fed into the machine is a genetic system of essentially complete simplicity. What is surprising is how fast rational information is produced by the machine within the meaning of the original context.

So, if you are going to take a program space and say, "We cannot transform it," but leave out of it the means of combination and recombination in between and of evolution by selection, I am certain that your program will not produce sense; but if you put it in there the machine gets there so fast it is surprising.

DR. SCHUTZENBERGER: What I have said is that insofar as principles have been explicitly stated, I have to deal with the whole space. To answer your question, one might believe that, in fact, life is using only extremely restricted subspaces of both spaces. What I am asking you, in all humility, is to provide me with a formal principle which would define those spaces, or to provide me with conceptual examples in which such spaces could be defined, even at the very modest level where they would have all the nice properties of matching. This has been done in a sense, at the Sewall Wright level: that is, on the space of parameters which by construction is correlated with the real world space. What I say is that such a type of restriction needs new conceptual tools, or principle, or what-have-you.

The Chairman, DR. WADDINGTON: I want Dr. Weisskopf to speak, but may I recommend that you have a talk in private with Alex Comfort; you can do it on his computer.

DR. WEISSKOPF: I want to analyze the difference of opinion between Schutzenberger and the rest of the world. This is, I think, the following: Schutzenberger says that in the typographical space, the overwhelming number of changes that can be done at random have absolutely no meaning, and he puts in support of it the fact that if you have a computer, and you change the program at random, it always is destroyed.

The other side says that that isn't so. The kind of program which genetics has produced with the 3-letter code is such that it isn't so. I think that is what Lewontin says, that a lot of changes, maybe not an overwhelming number but a large percentage, do make sense in the biochemical sense of the word, and here I think is the discrepancy.

DR. SCHUTZENBERGER: There is no discrepancy. I am asking for you to tell me what principle to use.

The Chairman, DR. WADDINGTON: I regret we will have to leave this discussion at the moment; I think Dick Lewontin's is the next paper.

The Principle of Historicity in Evolution

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I am not going to speak about the matter that is announced, "The Role of Selection Between Populations", because I am very tired of that topic, having spoken about it too often.

I want to talk about something different, something that has bothered and interested me for a short time that I think is more to the point of this symposium, anyway. I don't know what title to give it so I will try "The Principle of Historicity in Evolution."

It is a problem that arises for the neo-Darwinist, especially the sort of mechanistic neo-Darwinist who is concerned chiefly with predictions at a very simple level of the kinds of changes that will occur in populations.

It is usual for population geneticists, who claim that they are studying the dynamics of evolution, to divide the kinds of models that they deal with into two sorts. They talk about deterministic models and about stochastic models. What is meant by deterministic models is that, given the initial conditions of the population, which I will simply specify by X_0 (although that will be some sort of a vector of conditions of the population), and some set of parameters, S, then it is possible to predict exactly the condition of the population at some other time, τ. Then, we can specify exactly by some large set of differential equations precisely how the population is transformed in time.

What we mean by a stochastic model is, again, the conventional meaning of stochastic models. Given some initial vector which describes the population, we can only specify a set of probabilities of various final states at time, τ, but we cannot specify which of these will occur. These probabilities are calculable by probability laws which contain the parameters. That is simply a two-minute description of the present structure of population genetics.

There is, however, a complication that cuts across the characterization and one which gives us a great deal of trouble. It especially arises when we think of the stochastic model; but, in fact, it arises both in deterministic and stochastic models. It is most easily seen if one distinguishes the two aspects of study—not deterministic and stochastic, but kinetic and equilibrium aspects of the study of evolution.

The equilibrium aspect is the study of the state of the system X at some very remote time when it is assumed that it is not changing, or that it is undergoing some oscillation which can be analyzed in terms of a finite number of Fourier analyses. The system is in some kind of an equilibrium, whether it is a constant value or it is fluctuating in some constant way. There is a great deal of effort in population genetics and evolutionary theory devoted to the necessary and sufficient conditions of stable equilibrium for these processes.

Whether we assume that the selection coefficients, the parameters themselves, are fluctuating or that the population is finite and, therefore, has a stochastic element, the equilibrium that we talk about in stochastic models is, of course, not an equilibrium state but a distribution of probabilities of states. So we can talk about the ergodic properties of a stochastic model and say that at equilibrium there is some final probability π_1 of being in state 1 and another probability of π_2 of being in state 2, and so on.

I want to say that these equilibrium studies, whether we are talking about a stochastic or deterministic model, but es-

pecially when we are talking about a stochastic model, are descriptions of what I call a *space ensemble of populations*. One can say nothing about a specific population but can only describe the probability that a population will be in each of these various states.

The kinetic and stochastic theory of Sewall Wright and his school has been concerned with predicting the way in which this ensemble of populations changes in time (the kinetic aspect) and with what its equilibrium state is. For example, suppose we begin with a large number of populations, all at a gene frequency of .50 at some locus, then the kinetic aspects of our stochastic model predict that in the next generation there will be some spread in the distribution of this frequency. In the generation after there will be yet more spread, and so on. Finally the equilibrium aspects of the study predict what the equilibrium distribution of populations will be, what the ensemble will look like. This is statistical mechanics and, in fact, one can use certain methods of statistical mechanics for this problem.

If one thinks about it for a moment, he realizes that the information about the time transformations of ensembles of populations is really not very interesting for the evolutionist. He does not really want to know what the probability is that a population will have a gene frequency of .47 in some generation because he does not have a million or trillion populations to survey. No, that is not the problem. The problem is, What is the time ensemble of states of a given population? In fact, the confusion between the time ensemble of states and what I call the space ensemble at a given time, τ, is rife in population genetics. People usually make the assumption that if I can specify the space ensemble of populations at a given time, especially at equilibrium time, I am saying something about the probability that any given population has passed through one of those states in its life history, and that it will pass through one of those states in its future life history. But this is not true.

Let me illustrate this point by showing you a couple of space ensemble distributions that apply to a specific genetical problem. The genetical problem is, How do we explain the distribution of the frequency of a certain deleterious gene in the house mouse?

I will not go into the biology of this problem, which is not really essential for our purposes. Needless to say, certain predictions are made about the frequency of this gene in natural populations, and these predictions are not fulfilled. It seemed to us that the reason they are not fulfilled is because we have ignored a stochastic element in the process, namely, the fact that mouse populations are very small. So, in order to see what the space distribution of the ensemble would be, in order better to understand why it is that some populations have one gene frequency and other populations have another gene frequency, we simulated the process in a computer. I want to show you the kinds of results that a computer gives for this kind of simulation because it illustrates what I mean by the kinetic and equilibrium aspects of the space ensemble.

What is illustrated in any one of the small diagrams in Fig. 1 is the space ensemble at a given time, namely, the tenth generation, or the twentieth or the thirtieth, and so on. A population was started with a gene frequency, $p=.75$, and the process of natural selection and Mendelism was allowed to go on for 200 generations. The value of the gene frequency p was calculated for a given population in each generation.

Then, this procedure was repeated over and over again, about 100 times, so that we have 100 populations in each generation. Some of those populations have one value of gene frequency, some have another. So we see here a distribution of values over populations.

It can be seen that the distribution of the ensemble changes as time goes on, that there is an evolution of the ensemble, and that it then reaches a kind of equilibrium situation.

It should be noticed that one of the columns, at the value $p=1$, is growing larger all the time. These are the populations that have lost the segregation of the genes that are fixed at 100 percent of one type. The frequency of that state keeps

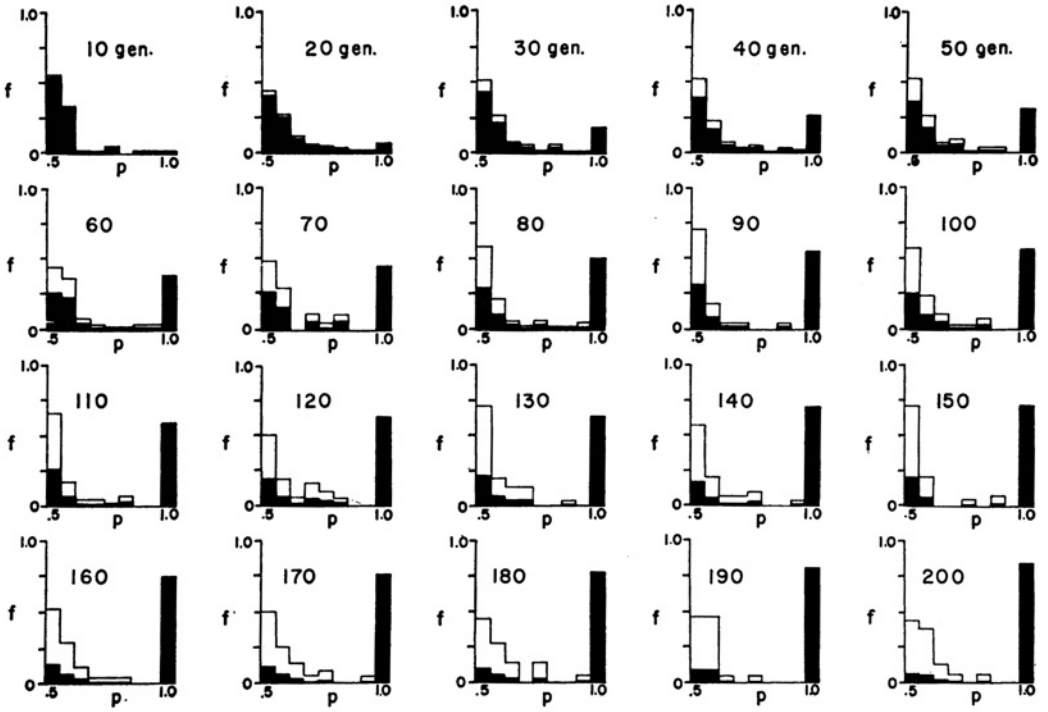

Fig. 1. Frequency distributions of gene frequencies in successive generations. The ordinate shows the proportion of all populations (runs) having a given gene frequency. The abscissa shows the values of p, the frequency of the normal allele. Black bars are the distributions of all runs. Clear bars are the conditional distributions for unfixed classes.

getting bigger all the time; but if we look at the distribution of populations not including that class, the conditional distribution of the unfixed ensemble (shown by white bars), we see that it reaches a kind of equilibrium situation. It wobbles quite a bit because the sample size has become quite small. Most of the populations are fixed in the terminal class; but, in general, no obvious trend is occurring. There is a unimodal distribution with a pile-up at p=.5.

DR. WEISSKOPF: Is there any difference between the black and white (Fig. 1)?

DR. LEWONTIN: The black is the actual distribution of all populations; the white is the conditional distribution of the populations not included in this last category. There is no difference in the conditional distribution from time to time.

Figure 2 shows for different parameter sets the form of the equilibrium conditional distributions of the ensembles after many, many generations. Set 5 and set 6 are pairs that differ in no respect except their initial conditions. In set 5 we began with populations that had a high gene frequency, near .5. In set 6 we began with populations with gene frequency nearly 0.1 and you see their equilibrium distributions are the same. In fact, there is no statistical difference between them. Sets 8 and 9 show exactly the same thing. So, these distributions are of the nature of stable equilibrium distributions of ensembles in time; it doesn't matter where you start the populations, they come to the same state.

This is an example, then, of what the population geneticist means when he talks about the distribution of states of populations. If there are thousands of these populations, what is the distribution of their states; how does that distribution change and what is the ergodic state?

Please notice that this solution is applicable to this particular problem about house mice because there are lots of small populations of house mice. I am particularly interested in the question, "Why is it that some populations of house mice have a low gene frequency and others have a high one?" I can compare the theoretical distribution with some distributions in nature,

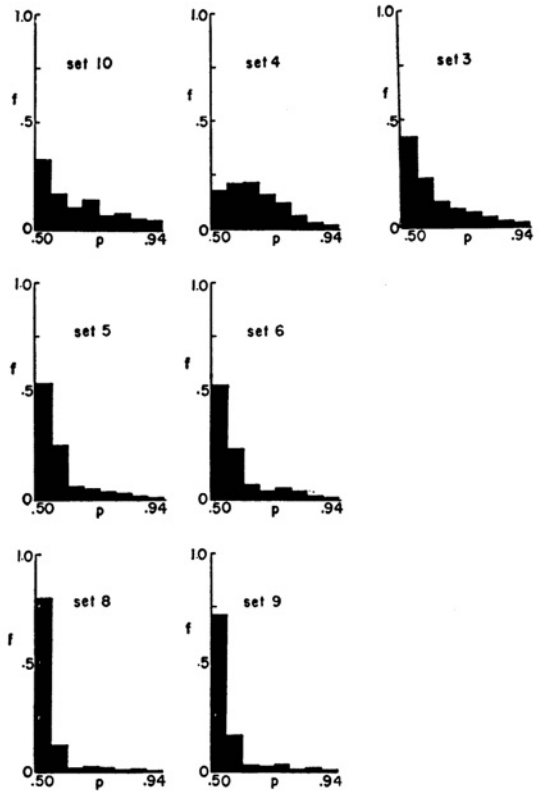

Fig. 2 Stable distributions of unfixed populations for various parameter sets.

as has been done by Paul Anderson in Alberta, and find as he has that these calculations are very good predictors of the space ensemble in nature.

When we come to the time ensemble of one population, instead of the space ensemble of replicated populations, we run into a very different set of problems. Dick Levins and I were doing some calculations on the board and we can just use these calculations, I think, to illustrate the point. Let us imagine that we have a population in which we are concentrating on only one genetical locus with two alleles.

We assume that one homozygote say, *aa*, has a relative probability of survival and reproduction 1—2S, as compared with the homozygote *AA*, the heterozygote being exactly halfway between. Now we have a simple case of no dominance, and S can be either positive or negative. When it is positive, the genotypes *aa* and *Aa* are being reduced in frequency, and when S is negative, these two genotypes are increasing in frequency. The equation representing the relationship between the frequency of the allele *a* in one generation, Q_t, and that in the next generation, Q_{t+1}, is:

$$Q_{t+1} = \frac{Q_t - SQ_t\,(1 + Q_t)}{1 - SQ_t\quad(1 + Q_t)}$$

What we suppose is that S, the selection parameter, is fluctuating from generation to generation; instead of being constant, it has some distribution in time. We are concerned only with a single population, and we ask the question, "What do we have to know about the distribution of S in order to ask realistic and interesting questions about the time history of Q and its distribution, its ensemble distribution in time?"

Without becoming more abstract, I want first to illustrate what happens with some numbers in a kind of meta-experiment, and then to say something general about it. What I want to show are the results of applying this formula to a population that begins at some time, zero, with a gene frequency of .5 We have a single population in which S, the selection parameter, fluctuates between +.5 and —.5, with a uniform distribution. When S is +.5, one homozygote is lethal. It has a zero probability of reproduction and survival. The heterozygote is halfway lethal. When S is —.5, this same homozygote *a a* is twice as fit as the other homozygote. The equation, as you see, is not entirely symmetrical in S, so there is a little bias in one direction; but, without the denominator, which is a normalizing factor, the process is symmetrical in S.

DR. WEISSKOPF: It jumps around statistically every generation?

DR. LEWONTIN: That is right, and the assumption that I have made is that the process generating S, the selection coefficient, is a random process with no serial autocorrelation; and that is a very important point. If I show any correlations, as I will, they will be generated not by the S itself, but by the nature of the genetic process. I just choose an S at random out of a population that is uniformly distributed between —.5 and +.5.

Let me first illustrate an important property of S. S is a random variable chosen from

a distribution with finite moments, and it falls under that very general and powerful law, the Law of Large Numbers. This law states, in this particular case, that the average value of S, if accumulated over time, will approach some fixed value which is the true average value. Generally the accumulated mean will approach the true value from one side. That is, if the first three values are all positive, say, then all the accumulated values tend to stay positive, but they deviate less and less from the mean as time goes on. Figure 3 illustrates this point. The two solid lines represent the accumulated mean of a set of random numbers taken in two different orders. The broken lines are the cumulative means for a different set of random numbers, again taken in opposite order from each other. Both the solid and broken lines should finally get to the same place; but one aspect of the Law of Large Numbers is that after you have accumulated many observations, then more observations don't change the mean very much. Every student knows that if he has failed the first ten tests, it won't do him much good to get 100 percent in the last one. Note, too, that the order in which the numbers are taken has little effect.

When we look at the next diagram (Figure 4) which shows what happens in population genetics, we get a rather different picture. The X's mark the values of S, the selection coefficient, that I have chosen at random; and you see that about half of them are above the axis and about half of them are below. There is no autocorrelation among them; they are, indeed, independent samples.

The solid line shows the course of history of a population whose gene frequency was initially .5 and which was selected according to the formula given above with the sequence of environments given by the X's in the figure. Gene frequency is shown at the right-hand side of the figure and the values of S along the left-hand side.

The population rose in gene frequency for a while and then there was a sequence of adverse environments for this gene so

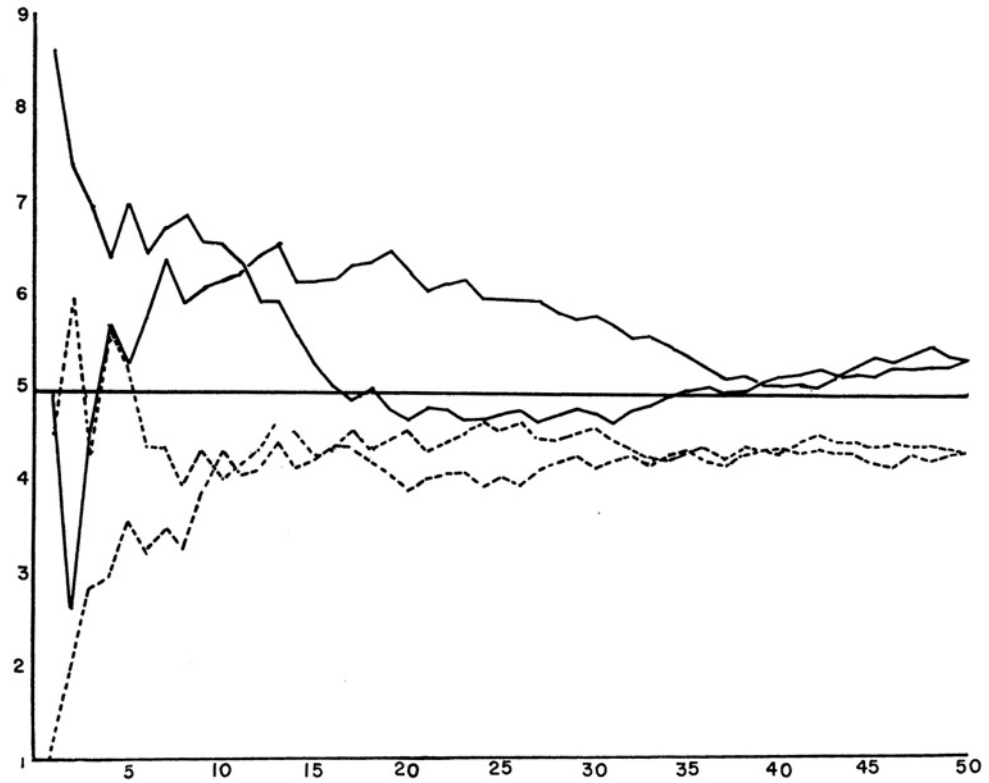

Fig. 3. Cumulative means of different sequences of random numbers. Ordinate: cumulative mean; abscissa: length of sequence. The two solid lines are one set of random numbers in two different orders, the dashed lines are two different orders of a different set of numbers.

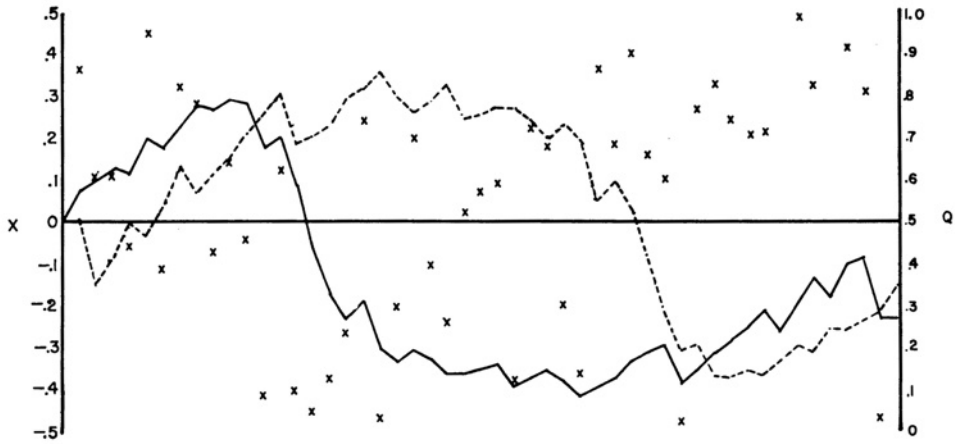

Fig. 4. Gene frequency (Q) of successive generations in fluctuating environment (x). Crosses are environmental value. Solid line: gene frequency in successive generations caused by environments given by the crosses. Dashed line: gene frequencies resulting from same set of environments in reverse order.

that the gene frequency dropped below 50 percent, and then there were still more adverse environments so it stayed below; but then there were a lot of sequences of environments which happened to be above the halfway point and so the population began to come up again.

You see that it has spent most of its time at a gene frequency below 50 percent and that if I drew the time ensemble of states, it would be skewed over to the left with a mode less than 50 percent, since most of the time the population gene frequency spent below 50 percent.

The broken line is exactly the same population, having its history traced for exactly the same set of environments, but in reverse order. Imagine that all the X's are reversed in order, so that the first environment is given by the last X.

The broken line population, in fact, spent most of its time, or at least a good proportion of its time, above the 50 percent point rather than below. The time distribution of this ensemble is skewed toward higher gene frequencies. Not only the sequence of events, but the time distribution of the ensemble of gene frequencies is completely different for the second population from that of the first one. This is so despite the fact that they have undergone exactly the same set of environments, simply in a different order.

Thus, if we are to understand the time distribution of states of a population, where a population spends most of its time as far as gene frequency is concerned, we must know more than the average selection against a gene and how variable that selection is. We must also have information on the time sequence of these environments. It is for that reason that the time distribution of environments, or, rather, the time distribution of states of the population, is different from the space ensemble which I spoke about before. It is for this reason that two populations living in precisely the same kind of environment—and by "same kind" I mean in which the probability of selection in a given direction has the same distribution in both—will nevertheless have totally different life histories. Not different simply in the sense that in a particular year one population was increasing in gene frequency and the other decreasing; but that if we went back, we would find one population with very high gene frequencies and the other population with very low gene frequencies, year after year. This would hold despite the fact that both populations are living in environments chosen at random from the same distribution of environments.

So, the historical accident of the order in which the environments occur necessarily changes the long-time life history of a population. The reason for that can be seen rather simply in the nature and the kinetics of gene frequency change. In general, we can write gene frequency change in any

population per unit of time as Q (1 — Q) times some function of the selection coefficients and Q, which is always of the first order in Q or higher. Thus the change in gene frequency is sensitive to the product Q (1 — Q). This is simply a familiar fact that if the population has a gene frequency very close to either 1 or 0, it is tremendously insensitive to selection. Let us say that for some period of time selection coefficients have all been roughly in the same direction, then the population will find itself at a gene frequency close to 1, where Q (1 — Q) is almost 0; and thereafter, even if selection operates in the reverse direction, there will be a very small change downward. If I look at the gene frequency at this time, τ, it gives me no information, or virtually no information, about the sequence of natural selective events in the previous short time. That is to say, a gene frequency that is close to fixation contains no information about the recent past; it contains chiefly information about the remote past.

On the other hand, a gene frequency that is close to 50% contains chiefly information about the recent past and essentially no information about the remote past. No matter what the remote past was like, once the gene frequency gets near .50 it becomes very sensitive to local fluctuations. So we have the curious fact that the amount of information contained in the population gene frequency about past environments depends on where the gene frequency actually is in the gene frequency range. Intermediate gene frequencies tell us a lot about the recent past, namely, that in the recent past selection was probably not too strong in one direction for too long. Populations with gene frequencies near zero or one have essentially no information about the recent past; you can't tell anything about what has been happening lately.

This brings me to a final point about historicity in natural selective processes that I think we ought to consider. This comes back full circle, as any proper play does, to the initial distinction I made between deterministic and stochastic models. A deterministic process I said, is one in which one could predict exactly the final outcome, knowing the original value and the relevant parameters. In other words a deterministic process has in it perfect information for a sequence of length 1. If I just give you one history of a deterministic population, because it is deterministic I can say everything about its past; I only need one population. It doesn't do me any good to have two, three, five, ten, or fifty or one hundred because there is no stochastic element. All the information is contained in the history of one population, so we can have perfect information in one example.

A stochastic process is one that behaves according to the Law of Large Numbers. It is a process such that the information about the universe increases as the size of the sample increases, and finally approaches unity as the size of the sample goes to infinity.

This is a slightly more restricted definition of a stochastic universe than is usually used. I am going to insist that a stochastic universe is one that behaves according to the Law of Large Numbers. More specifically, my information about the universe increases to perfection as the size of the sequence goes to infinity. The deviation between the observed sum and the true value grows small with a probability arbitrarily close to unity.

I want finally, then, to talk about a capricious process, which is a third kind of process, not usually described. A capricious universe is one in which the receiver of information (it doesn't say anything about the universe itself) cannot get perfect information about the universe, no matter how long the sequence of events. A capricious universe, from the standpoint of the observer, is one in which, no matter how much he has learned in the past, something unlikely or something unexpected is likely to crop up; moreover, it doesn't matter how much longer he learns, he won't learn anything more. He won't be able to be a better predictor, even though he accumulates a lot more input.

What I claim is that genetical processes in time are of the nature of capricious processes. It does not matter how long the sequence of environments may be, the population gene frequency is not learning more and more about the environment. On the

contrary, there is an equilibrium amount that is learned about the environment because the correlation between the present state of the population and the past selective history falls off with remote time too rapidly. So, in fact, if the population is at a very low gene frequency, it doesn't help it that there may have been a long period in which selection was, let's say, in the positive direction. Population gene frequencies do not behave according to the Law of Large Numbers. Therefore, the gene frequency in the population cannot be said to be a perfect information storage device about past environments.

I don't want to press this any further. It is a suggestion, then, that what we need to do, from a mathematical standpoint, is to solve a quite different equation, or set of equations, than we are used to solving. Ordinarily we would solve the equations which tell us the equilibrium distribution of states in space of the space ensemble. This, generally, is something I will call Φ (Q), the distribution function of the gene frequency at equilibrium. This is usually found by the standard methods of stochastic processes, namely, by describing the change as a partial differential equation in time, and solving that partial differential equation when possible. As some of you know, this has been done a lot in population genetics by analogizing genetical situations to a diffusion process and using the Fokker-Planck equation to find ergodic properties of the distribution.

Instead of that, we need to ask a different question, which is: If I can describe a process, S, of selection in time, I must know not only the moments of the distribution of S as the statistical ensemble without time, but I must know something about the covariances in time, and perhaps more. I certainly need to know the variance of S and mean S. I am suggesting that I also need to know the covariance between S and S^1, S in two successive generations; and I may need to know more than that.

With that information, I want to derive θ (Q), the time distribution of the Q values, a description of the time ensemble of states.

What I need to do, then, is to be able to answer the question: "What is the probability that a given population will have a gene frequency Q if it is undergoing a fluctuating selective history where the selective history has certain parameters?" That, I repeat, is not to be confused with the space problem, which is, "What is the probability distribution of population gene frequencies at a given time, if it is assumed they all are sampled from the same selective process with a random element?"

Discussion

PAPER BY DR. LEWONTIN

The Chairman, DR. WADDINGTON: In the remaining time, what I propose we shall do is to have, first, a bit of discussion of Lewontin's paper. I am not going to give a paper concerned with anything I circulated. I will try to bring out the major questions that have arisen, the major discussions between the mathematicians and the biologists, and see if, after a night's thought, we can clarify any of the issues or at least define what the disagreements are, even if we can't resolve them.

I should like to start the discussion by asking, Is it the case that if you acquire information by sequential samples of any process that involves a stochastic element, this information will be capricious; is capriciousness simply an historical aspect of the stochastic process?

DR. LEWONTIN: No, because it depends on information about what. For example, if you have a mechanism for accumulating the mean, then you will eventually have perfect information about the mean. If what you want to know is the true universe mean and you have some method of tabulating all this information by just taking the cumulative sum, then it won't be capricious. In

fact, we must distinguish those things for which your information-accumulating mechanism behaves according to the Law of Large Numbers; namely, the longer the sequence, the more you know. In statistics, this is the notion of the consistent estimator, the one which gets closer and closer to the true value, the bigger the sample.

The Chairman, DR. WADDINGTON: Yes, but this is information about the global system.

DR. LEWONTIN: Yes, but it would be about the next value.

The Chairman, DR. WADDINGTON: The paper, in general, is open for discussion.

DR. WALD: I would like to ask a question here before you get down to serious business. Would it be oversimplification, Dr. Lewontin, of the earlier part of your discussion to say that it makes recapitulation kosher again? Since there may be some misunderstanding about what I mean by recapitulation, it is just the retention of past history, quite apart from adaptive considerations; for example, those eels migrating to the Sargasso Sea.

DR. LEWONTIN: I guess recapitulation is an evidence of an information storage mechanism in which there has been what might be regarded as internalization of some very long repeated trends in evolution. I would prefer to think of a simpler case—I think it is the same thing—the case of the obligate rather than the facultative alternator of generations. There are some parasites which change from sexual to asexual only when they change host, and that may be a variable number of generations; but there are those where, like it or not, there are two asexual generations and one sexual, or something of this sort and such parasites must change host at the same time. I would regard those as having a built-in clock which says, "In your past history you have been kicked out of your primary host so often that you had better go sexual immediately, because it is going to happen to you again!" I think there must be cases where long-repeated alternations of a fairly simple kind have been built into the organisms' life history pattern and this is a kind of recapitulation of past developmental history.

DR. WALD: Recapitulation in the sense of storage of past history seems to me self-evident; but its self-evidence perhaps lays it particularly open to suspicion. It seems to me self-evident that organisms carry along residues of their past history that they can continue to live with. They discard what they have been forced to discard, but retain many characters that they simply haven't been forced to discard. They carry such vestiges along as a kind of ritualistic luggage.

DR. LEWONTIN: Let's put it this way: by the somatic history of individuals, by the somatic adaptation of an individual, he can include lessons from the past which a population as a dynamic ensemble can't. This is, after all, what canalization and homeostasis are about. They say, "Since the population has a dynamic which cannot include all the past information because the gene frequencies are changing, then the way to protect yourself against recurrent events is to have built-in, as an individual, certain buffering mechanisms."

DR. ULAM: Statistically this sort of thing does happen. Studies of interacting species have been made, i.e., mathematical formulations have been made by Volterra and others. They often show a periodic behavior in time, i.e., the number of one species goes up and the other goes down and then the thing reverses. There need not be a limiting steady state with fixed ratios of the various populations.

The Chairman, DR. WADDINGTON: Well, that is included here.

DR. LEWONTIN: Yes, I included equilibrium oscillations, of course.

The Chairman, DR. WADDINGTON: I think the point that follows from your exposition in relation to recapitulation is that you can't really incorporate the history of the remote past into anything that you require to vary. You can only do it when you fix the gene frequencies at 1 or 0. If you have to have variability in the character, you can only refer back a few generations. Your past history is sloughed off.

DR. LEVINS: In distinction from the engineering systems in which you can have an information-gathering system and a separate output which uses the information as you

wish, in the genetic system the information storage *is* the gene frequencies; but the output also depends on these gene frequencies, and the requirements of the two are to some extent contradictory. In fact, it is advantageous for a system to forget a lot about the remote past if it is the recent past that indicates what is coming.

This raises the question, How much should it forget? Lewontin concentrated on the pattern of the environmental sequence and, therefore, he showed a single genetic model. We also know that different genetic systems have very different kinds of memory behavior. We have complex linkage that can wait ten generations before starting to respond, for example; and, therefore, we can have systems of varying degrees of memory which seem to be related, or at least their adaptive significance seems to be related to varying degrees of coherence, to the environment and time.

DR. FRASER: It seems to me that, with this presentation of Lewontin's, we are getting on to an aspect of the whole symposium which is well worth developing more fully, namely, the fact that the genetic system is actually an extremely efficient learning tool and can be contrasted as such with the experiments on learning which have been done within computers. I would like Lewontin if he would, since I am sure he can do it better than I can, to expound on that.

The Chairman, DR. WADDINGTON: Since time is getting on, I think it would be a good thing if Fraser came and told us something about some of his computer experiments with the genetic system as a learning machine. This will carry us on, I think, to the sort of general discussion which we want to have at the end.

DR. FRASER: Most of the efforts on learning in computers have been based on the random change of a sequence of letters with periodic tests to determine whether the sequence has been varied into a functional form.

This can be contrasted with a genetic system in which you are similarly putting in a random sequence, but with a pre-set logic of how it is to be transmitted and how much of the information gained in any one generation is to be dissipated between generations. The genetic system, if diploid, has the feature of recombining two random sequences to produce a range of new sequences. If one is contrasting this with learning to write programs by a computer, then you would have to write the random sequence of letters in parallel, with a pre-set logic: in transmission from one cycle of test to the next, the computer would read along a sequence and if it did not make sense, it would go back and read the parallel line. If this did not make sense, it would then start reading down one line, crossing over to the other line to complete the reading.

The whole system would not be dependent on a yes or no decision of value. That is, if you are working on learning in a machine, you would say, "Will you do *something* logical?", excluding "will you do something partly logical." The program either works or it doesn't, and this is your test of value.

In the genetic test, there is no absolute test; it is a competitive test at all points. In the transmission of information between individuals in any generation, it is those which transmit the most at any time which succeed. They may in actual fact be highly inefficient transmitters, but they are the ones that transmit the most; so that you are taking partial solutions at all these stages.

The introduction of parallel sets is not an algebraic fiction. Intragenic complementation has shown that you can have two genetic words, each alone being absolutely nonsensical biologically or enzymatically, but which in combination will use the sense bits from each, putting them together to make sense. Therefore, the geneticist, in his programming in a computer, is allowed to use the same process when he is transmitting information from one generation to the other.

It would seem to me that when one says that the experience on computers is that they are very bad learners, it is necessary to look at the basis, the restrictions and constraints you are putting on the whole process of test of learning. The genetic mechanism is a superb learning device in various ways, because if it finds a useful bit of information, it can fix this information at any stage so that it no longer goes into the

dissipation pool. The information is then maintained as a constant. It can then concentrate on its stochastic sampling through the other parts of the information and gradually build up a full sense message.

At any stage, it can evolve its own system of dissipation or nondissipation between generations. This is what Levins mentioned in terms of the actual transmission scheme of memory, that too much memory can be very bad, too little can also be very bad. One can evolve this on simple competitive value judgments. These are not absolute value judgments. I think Lewontin earlier made the statement that a species, at any time, is maximally adapted. I think this should be changed: It is minimally ill-adapted by comparison with competitors. There is no such thing as an adapted species. There is an adaptive compromise, which is the best compromise that one can reach at that time. Therefore, you are not dealing with absolute value judgments. You are always dealing with competitive compromises.

When one goes to a machine and says, "I am going to take as my analogy extremely inefficient man-made learning attempts, using stochastic sampling in computer programming," I think one has to contrast this with what is probably, algebraically, about the most sophisticated learning machine that one can come across, namely, the interaction of the genetic mechanism with the selection test.

The Chairman, DR. WADDINGTON: Would anyone like to disagree?

DR. SCHUTZENBERGER: I would flatly disagree, for the following reason, which isn't easy to explain here. I suppose that in most of those experiments, the space on which it is acted is a space of parameters, which is, at this time, a highly artificial and unrealistic model of anything which happens in the real world. It may be true that it is an extremely poor model compared to the programming of languages, but this model has at least one virtue, that we don't postulate more than we know to exist and that we reason on this explicit basis.

What I have said was, for the sake of simplicity, phrased in the language of typographic mistakes. It could just as well have been phrased in exactly the same manner using as units meaningful procedures. So what I said, again, does imply in a rather general context that there is no algorithmic procedure so far known to make sense out of nonsense, except as you have introduced it. It is hard for me to know what you have in mind, but what you have in mind is an entirely different object, a physical configuration in a Euclidian space, which is more unrealistic than random programming. I am sorry, perhaps I didn't make my point.

The Chairman, DR. WADDINGTON: Does anyone want to make a further comment on Alex Comfort's remarks?

DR. ULAM: I agree with the remarks which have been made. The whole process of development is like creating a language whose rules have not been formalized and whose vocabulary has not been stated in advance. The thing develops in a certain way and the very meaning of "sense" itself develops alongside or with it. There seems to be no a priori, or initially stated, definition of "purpose" or "sense". There is no absolute.

DR. FRASER: No absolute?

DR. ULAM: Exactly. The whole set of criteria is relevant only with respect to the changing situation. One test, which is seemingly absolute, is merely surviving.

DR. FRASER: There is one absolute. It must be capable of transmitting.

DR. ULAM: Yes, this is a very important point.

DR. SCHUTZENBERGER: Transmitting what to what?

DR. ULAM: To itself.

DR. SCHUTZENBERGER: Produce a formal model.

DR. ULAM: But the whole point is that there was no formal model given in advance a billion years ago from which one would be able to predict what would develop. The very rules of development were changing in time and influenced by the changing external condition.

DR. FRASER: I can give a model, I think. You have a sequence of letters in a computer programming bank. You require somewhere in the whole of that sequence of letters, but only in one place, any place will

do, to have the statement read out "punch cards for input." This is a fairly complicated message. If you try to do this by random changes, somewhere along the line you are requiring an extremely difficult solution of high improbability. However, if you arrange this so that the message is split into two long strings of letters running side by side and if there is any sense in one bit it can now examine the neighboring string to see if the logic continues; it has doubled its sequence. But, if it is allowed to pick up two partial senses and to combine them for sense on a logic which experimentally we already know to exist, then, as of that moment, such cross-reading allows us a greater potential in learning. The logic itself is not being produced out of our heads; we know it exists, the organisms have biologically shown it to exist.

DR. ULAM: The very meaning of sense evolves.

DR. FRASER: Yes.

DR. SCHUTZENBERGER: I am sorry; I want to take the floor again. We are forced into somewhat dogmatic assertions, so I would prefer that we agree on statements on your side on which I could base my own assertion in parallel.

Would you agree that making a message meaningful for any environment means making it able to evolve or to grow something in a certain order so that selection can be applied. If so, my question is why this pool of proteins is meaningful.

The Chairman, DR. WADDINGTON: What do you mean by "meaningful"?

DR. SCHUTZENBERGER: By "meaningful," I just mean which doesn't jam the system.

The Chairman, DR. WADDINGTON: Which can be transmitted?

DR. SCHUTZENBERGER: Which can be transmitted, if you prefer.

DR. FRASER: No, no, you are confusing "meaningful."

DR. SCHUTZENBERGER: Which can be transmitted; or another way would be to say, which is such as to give rise to enough epigenetic action so as to be sifted and improved.

The Chairman, DR. WADDINGTON: That's much more complicated.

DR. FRASER: As I said, the program must work completely or I will accept no solution. If, however, you tell it, "My acceptance of solution is partial and stepwise," at that point your first requirement is: "Program, read yourself."

DR. SCHUTZENBERGER: O. K. Would you accept that it is as rare or as frequent as the production of grammatically correct sentences? I am not speaking of randomness. I am speaking of size of sets. We take the set of all conceivable strings made up of English words; some of them are grammatically correct; some of them are less so, mine, for instance; some of them would be utterly meaningless.

It seems to me that in order for the pool of instructions—enzymes, proteins, procedures—to be meaningful it needs as much constraint as is needed to produce a grammatically correct sentence in English? Would you agree to that?

DR. BOSSERT: No.

DR. FRASER: Not at all.

DR. LEWONTIN: It takes a lot of constraints, there is no question.

DR. SCHUTZENBERGER: I am asking a question; we must work on some basis. Consider a pool of enzymes—let's forget about this molecule business—a pool of enzymes or a pool of any biological modules. In order to work long enough to transmit information, or to be operating within the epigenetic mechanism of our Chairman, do you believe that among all the possible configurations which could be, the ones which have this modicum of viability are more or are less frequent than the meaningful or grammatically correct sentences, among all possible strings of words? This is a question, a factual question, that you can answer with a yes or no.

DR. WALD: Are you asking what programs the genes?

DR. SCHUTZENBERGER: No.

DR. FRASER: No, no.

DR. SCHUTZENBERGER: O. K., let's waste time.

DR. FRASER: We understand the question.

DR. LEWONTIN: The answer is no.

DR. FRASER: I can give you an example.

DR. LEWONTIN: The probability of making a random change—

DR. SCHUTZENBERGER: I am not asking about the probability of making a random change. I have a set—

DR. LEWONTIN: It requires some constraints but not as many as in your English language, that is all. If I take words out of the dictionary and put them together, they are less likely to make any sense at all than if I take the known enzymes in an organism and change one.

DR. MAYR: Much less.

DR. WEISSKOPF: That's quite different.

DR. LEWONTIN: The two processes are different. We are not constructing organisms by throwing enzymes together at random.

DR. SCHUTZENBERGER: Look, I am not using the word "random," so either stop using it or define what you mean.

DR. BARRICELLI: Could I show you an example which would be to the point?

DR. SCHUTZENBERGER: No. What I am asking is not a factual question, but it is a question. On the other hand, there is the set of all strings which could be made out of English words. Within this set there is a certain sub-set of those strings which makes an understandable sentence. I would agree, for technical reasons, that these are the grammatically correct ones, but it doesn't matter very much for my argument. So, this is a sub-set which is far smaller. We have reduced logic, so far as I understand, to a bag of enzymes.

DR. WALD: No.

DR. FRASER: Go further back.

The Chairman, DR. WADDINGTON: Go ahead with your diagram.

DR. MAYR: Do whatever you want.

DR. SCHUTZENBERGER: Thank you. I will do it in any case.

You should be able to provide me with a formal definition of what should be the set of objects out of which the living organisms are defined.

The Chairman, DR. WADDINGTON: DNA.

DR. SCHUTZENBERGER: It comes under the DNA chain at that level, and on the genes, I suppose. I am not very conversant with those matters.

In a reasonably complete theory, you should be able to define for me a class of systems out of which only a certain fraction would be the systems which can exist biologically, which are meaningful in a biological sense.

The Chairman, DR. WADDINGTON: We will define them; they are the set of DNA molecules in association with proteins. At this point I will stop discussion by summing up my point on this particular question.

I think what the biologist is saying in this connection is that we have a space of all possible nucleotide sequences with associated amino acid sequences, so that you have the DNA and the protein which you can consider as a complement. We are not concerned with mechanisms for translation but we will take the set of all possible complements of nucleotide and amino acid sequences.

This set was entered at the beginning of life, starting at some point or points and was explored to find sets which would operate adequately enough to ensure transmission. The space was explored to some extent, but always sequentially from the last position to some neighboring position.

As soon as it was explored enough to get sufficient of these couples together to work with fair efficiency, they became insulated from the whole of the rest of the space, because they would have eaten anything else before it had a chance to get going. Therefore, life has only explored a minute fraction of the total nucleotide space.

In the part which it has explored, which is the only part that is relevant to a consideration of evolution, biologists are asserting that the meaningful section of it is quite large in comparison with all the things that could conceivably be made out of it in single steps. It is a much larger fraction than is the space of meaningful strings of English words. I think this is the point. We are asserting that it is a large fraction of the total space which could be made from the nucleotides involved, but still we are saying that the meaningful space is a minute fraction of the total nucleotide space.

DR. BARRICELLI: I would like to mention an example which I think is quite relevant to what has been said here. In the virus T_4 we have two very famous genes, the rIIA and the rIIB. A large number of mutations,

many of them deletions, are known in these two genes. Benzer has found several hundred deletions. Each deletion results from the loss of a piece of genetic material. Its effect is to prevent the gene from working normally, thus causing a detectable mutation. Besides deletions, there are also other mutations, thousands of mutations, in these genes. A large portion of these mutations are caused by a missing nucleotide or an inserted nucleotide. Such an inserted or missing nucleotide would shift the reading frame, thus making a large portion of the gene useless (or nonsense). However, within certain areas of the rIIA and rIIB genes, two mutations of opposite type (one inserting and the other removing a nucleotide) can often compensate one another. What is more important, even deletions can in some cases be compensated by a mutation of this type. In other words, you can produce a deletion by taking away a piece, and the gene does not work. But then you can remove or insert a nucleotide at another point in the same gene, and it works.

You have an example of a deletion which extends from one point in the rIIA gene to another point in the rIIB gene, with the result that both genes do not work. However, you can add another mutation to it such that the remaining piece of the rIIB gene will work together with the remaining piece from the rIIA gene and make one gene which works only as rIIA. It doesn't work as rIIB in that case.

Essentially, in a portion of these two genes, it is a general rule that if you have removed one nucleotide in one place and added another nucleotide in another place to restore the reading frame, the gene still works. A part of it is out of frame but it still works. You can remove three nucleotides and it works. You can add three nucleotides and it works.

In other words, you have thousands of possibilities of correcting one mistake by another mistake in another place. This means, simply, that a large portion of these two genes can be removed or modified without observing any harmful effects.

Summary Discussion

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The Chairman, DR. WADDINGTON: That is an example. I think we will have to leave this question here now; we have defined what the difference of opinion is. It is the relative size of the total nucleotide space compared to the part of it so far explored by life, on the one hand, and the relation between the part explored by life and the subset of it which is meaningful, on the other.

I want to take up some of the other points. This conference has turned out not to be at all what its title was, "Mathematical Challenges to the Neo-Darwinian Interpretation of Evolution." It has actually been concerned with mathematical challenges to Darwinism as a whole, raising many points that were avidly discussed in the 1870's and 80's. The first set of these questions centered around numbers and arithmetic; has there been enough time? One question is in the field of gigantic numbers, and the physicists have thrown at us 10^{350}, and billions and trillions, and so on. Of course, biologists, particularly microbiologists, have been used to working in billions and trillions. Large numbers are really what we like. The great advances in modern genetics have just come from being able to work in 10^9 organisms instead of having to fiddle around with 100 or so mice. So mere large numbers are not really anything to be very alarmed at, I think.

The question that was asked on the first day was, Is there time enough for evolution? What seemed to me to emerge is that in a nonsexual process of reproduction, a purely vegetative system, in which evolution depends on waiting for a new mutation to turn up when it is wanted, you have an exceedingly slow process. One might really wonder whether there is time for it to get through. Of course, the first and greatest invention of life was sex, which solves the whole problem.

As soon as you get sexual reproduction and a combination of genetic information from two parental individuals with all the possibilities of recombining and shuffling around, the problem really disappears. As Professor Mayr pointed out, a new species may evolve in 100 years or so.

I think there is another point which biologists wanted to make here to their physicist colleagues about how these calculations about available time should be looked at. The point was made that to account for some evolutionary changes in hemoglobin, one requires about 120 amino acid substitutions. The calculations were done on the basis of treating these substitutions as individual events, as though it is necessary to get one of them done and spread throughout the whole population before you could start processing the next one. The whole thing had to be done in sequence; and of course, if you add up the time for all those sequential steps, it amounts to quite a long time.

But the point the biologist wants to make is that that isn't really what is going on at all. We don't need 120 changes one after the other. We know perfectly well of 12 changes which exist in the human population at the present time. There are probably many more which we haven't detected, because they have such slight physiological effects that there is no way of picking them up. I should think it is pretty safe to say that there are 20 different amino acid sequences in human hemoglobins in the world population at present, all being processed simultaneously, if they are going to be used in evolution at all.

Calculations about the length of time of evolutionary steps have to take into account

the fact that we are dealing with gene pools, with a great deal of genetic variability, present simultaneously. To deal with them simply as sequences of individual steps is going to give you estimates that are wildly out.

The other and I think more interesting problem, which we have hardly begun to solve, is the question: How many changes of information are necessary to explain evolution? This was put largely in terms of, How much information do you need to specify biological organisms or their functional parts?

Here I think the answer is that we have no method of estimating this at all; because it is quite clear that the specifications are in terms of instructions, algorithmic instructions. When you specify an enzyme which does something, you don't identify each point in space and specify its constitution. You are giving instructions for building operating agencies which may be cells, enzymes, or whatever you like.

I would like to show you a little model organism of mine which illustrates the point very nicely; everybody else has put up his favorite model. It was stimulated by Ulam's 2-dimensional patterns which he generates by a simple set of instructions, but this is a 1-dimensional one.

Consider a system consisting of three elementary units, A, B and C, which can be joined together into linear strings. Let the rule for determining the next member of a string be as follows: Given a string terminating at unit n, the nature of the next unit $n + 1$ is determined by comparing n with $n - 2$; if they are different, put the other, third type for $n + 1$ (e.g. C A B. .A); if they are the same, repeat the unit (e.g. B A B. .B). Apart from the three trivial cases AAAA . . . , BBBB . . . , CCCC . . . , the system has the property that, starting from any arbitrary triplet, you come to one or another of only three kinds of repeating sequences, each of eight units. These are AABCBBAC, AACBCCAB and BBCACCBA.

It is interesting to note what happens if you make a mistake. Putting the wrong letter down, e.g., a C where you ought to have put a B, does not produce a random effect; it merely switches you from one of the repeating sequences into one of the others. On the other hand, making a mistake in the algorithm has a somewhat more drastic effect, but again not a random one. For instance if you compare n with $n - 3$ instead of with $n - 2$, you find yourself in one or other of a set of six possible types of 13-letter repeating sequences.

The only point of this is to illustrate how you can generate a surprising amount of order with exceedingly simple instructions. If you are dealing with a system in which order is generated by instructions, changing things at random is not going to give you a random effect. It is going to give you one of the possible ordered systems of effect.

It is the fact that this sort of thing occurs that really makes it totally impossible to know how to formulate the question of how much information you need to make an eye. We just haven't got the theory about this at the present time. I was hoping some set theory experts or group theory experts would be here to give us some nice general principles.

DR. SCHUTZENBERGER: That, I can.

The Chairman, DR. WADDINGTON: That is a very, very simple example.

DR. SCHUTZENBERGER: I am sorry to be disagreeing with you so openly, sir, but if I were not taking you seriously, I would not. This type of object which you have described substantiates exactly my point. This mechanism is a type of algorithm which is called a finite state machine. What we claim is that finite state machines are incompetent for producing the effect which we observe in life. In linguistics, the same thing has happened.

The first people who tried to work out models of linguistic mock-up, for instance, invented finite state models of language. This is completely insufficient to make any interesting thing out of strings of letters. More is needed for linguistics, even for the simplest, barest type of linguistics. More is needed for making strings of procedures which work, which are meaningful in the sense that they can enter into a computer. We need far more complex algorithms, which cannot be finite state ones. They can be described with a finite amount of infor-

mation, provided there is already existing a highly elaborated mechanism in which the understanding of this meaning is there, is built in beforehand.

The Chairman, DR. WADDINGTON: Let me point out that I am not putting this sort of process into your genotypic space; this is in the epigenetic space. I don't say that mechanisms of this finite-state kind can produce meaningful information which can be transmitted. I am saying it plays a part in the translation from the genotype to the phenotype, and I am not merely saying this theoretically. I will give you a practical example.

If you dissolve collagen molecules and get them broken down to some extent, they will spontaneously reaggregate into a definite spatially ordered structure, which is a definite practical example that this can happen. It is an operation in the epigenetic system. When you say, "How much information do you need to specify an eye?"—the question you are asking is about the epigenetic system. You have a lot of information in the DNA, you have an eye in the phenotype. I am saying that between these two, much of this sort of mechanism may come in, which makes it impossible to estimate, merely from looking at the complexity of the eye, the complexity of the original instructions. That is all I am saying.

That, I think, is one of the very important points that has emerged. We can't quantify the theory of evolution in any sense until we can answer questions such as: How much information is needed to produce a given complexity of structure?

Do any of the other physicists want to make any remarks? Dr. Weisskopf, what would you have to say about this?

DR. WEISSKOPF: I very much agree with what you just said. This is what we have to know, either from you or from the mathematicians.

Let me ask one question of the biologists. I have often heard that actually the eye has been evolved several times, each independent of the others. If this is true, there is something in the statement that it is much easier to make an eye than we all believe.

The Chairman, DR. WADDINGTON: I think it is relatively simple to make an eye.

DR. MAYR: I don't know who should answer that but I agree there, too. Somebody quoted Darwin yesterday and, as with the Bible, you can quote him for one thing or another. In one place he said that it completely horrified him to think of the eye and how to explain it; and at another place he said once you assume that any kind of protein has the ability to react to light, once you admit that, then it is no problem whatsoever to construct an eye. If you have a light-sensitive protein, then by natural selection you obtain pigments, anything that changes the diffraction of light, and any kind of a lens-like substance. As a result—and I think there are conflicting statements in the literature—somewhere between twelve and seventeen times in the history of evolution, eyes have evolved independently, separately, in different lines of organisms.

So the eye simply means a light-sensitive structure with auxiliary organs like pigments, lenses and focusing devices of various sorts. I don't think this is as difficult to evolve as is sometimes claimed.

The nerve elements in the retina in many ways are very similar to nerve elements in other sense organs. There, too, this makes it difficult to quantitate the degree of novelty because the invention may have been made originally for some other sense organ and it is then just applied to the eye.

The Chairman, DR. WADDINGTON: Yes, it is also relatively easy to make an eye embryologically. What you have to do is to deform the tissue to turn it into an eye. From a relatively flat piece of tissue you have to make one part sink in to form a sort of spherical vesicle, and then you have to change the layer of tissue that comes on top of that to render it transparent, and possibly thicken it to make a more effective lens; but you have got an eye in relatively few steps.

I think the next great controversy was about the nature of the theory of evolution. Some physicists were saying it is not a real theory at all; either it doesn't explain anything or it explains everything. This is something I think we want to try to clear up. I tried to make the point that my own

view about this is that the theory of evolution is unfalsifiable, or at least very difficult to falsify, to the same degree that Newtonian physics is very difficult to falsify. The criticism was that if an animal evolves one way, biologists have a perfectly good explanation; but if it evolves some other way, they have an equally good explanation. So what is the good of all this explanation? If I find Jupiter has six moons, the physicists have a perfectly good Newtonian explanation; but if I find it has seven, this doesn't do anything to Newtonian physics which can easily produce a slightly different explanation which explains that just as well. This is exactly parallel to what is going on in evolution theory. This means that the theory is not, at this level, a predictive theory as to what must happen. It is a theory which tells you in what terms to analyze the contingent events you happen to come across; and this is the main aspect of Newtonian physics—that it tells you in what terms to explain any motions you come across. If you hit a billiard ball, it bumps into another billiard ball or it doesn't; if the angle of deflection is not normal to the tangent at the point of contact, then one of them must have had a spin, or it must have had inhomogeneous elasticities, or something. Newtonian physics doesn't exclude this sort of thing happening. It simply tells you in which direction to look for the explanation.

However, I do think Victor Weisskopf posed a really crucial question for us when he said: "Quantum physics is quite largely unusable because most problems are too complex to work out; but you can solve the emission spectrum of the hydrogen atom, and so you really believe the thing all the way through because there is this one case in which, starting from first principles, you can work out precisely what the emission spectrum ought to be." Then he asked, Where is the hydrogen atom of evolution theory?

First I would like to point out that in the quantum theory, as I understand it, you can't actually work out the emission spectrum of one hydrogen atom. You work out the emission spectrum of an assemblage of hydrogen atoms, but with any given one you can't really cope with it. So, it is not as strong a theory as all that, when you come down to it.

But now can we in biology provide any examples in which the theory allows us to predict the answer? I should say we can provide hundreds of them. I think we can predict that if you use a new insecticide on a fly population in Madagascar, these insects will evolve resistance to it within a few generations; this is a perfectly good evolutionary prediction. Well, it is not perfectly good. It *begins* to be an evolutionary prediction. We can't predict in what way they will do it. They may get resistance by increasing the impermeability of their cuticles, or they may get resistance by inventing some new enzyme that detoxifies, or by a variety of mechanisms. We can't tell by which mechanism, so it is not a perfect predictive system; but it has some predictive value.

DR. LEWONTIN: We could, of course, improve that prediction even in the way you are stating it by first examining the population to see what kinds of variations are there with respect to these characters.

The Chairman, DR. WADDINGTON: Yes, I was going to come to this, because one other point is this: before you start doing experiments to see whether the emission of hydrogen is what you think it ought to be, you go through a fairly elaborate process of preparing for yourself some pure hydrogen; and this is normally what the biologist either doesn't or can't do. He can do it in Drosophila; he can set up a population with genetic parameters of such a kind that they allow you to predict the answer. To some extent, I did this in some of my selection experiments. I selected a population so that it was extremely easy to modify its phenotype in some given way. Then a random gene mutation turned up that did modify the genotype in this way in this population, where it has been made easy to do it; but I couldn't make this modification in other populations where it had not been made easy to do it. In a way, this is somewhat comparable to purifying your chemicals before starting a physical experiment.

So, I don't think the difference between the theory of evolution and the physical

theories is really quite so radical; but now let me turn this over to the physicists and see whether this has convinced them at all.

DR. EDEN: I wonder if I could make a couple of comments on some of the earlier points you made. First of all, I think we have to be very careful about what we mean by large numbers. There are large numbers and there are very large numbers. I have a little anecdote which may be to the point. Professor George Gamoff in a class in relativity posed the following example on the use of large numbers. He said, "Suppose you were the captain of a spaceship and you were on an expedition to verify that the universe is 10^{11} light years in dimension. You have been going now for very close to 10^{11} light years and you should reach the edge of the universe in a day or two. Suddenly the navigator sends a messenger to you who says, "I have made a minor mistake in my calculation. It is really 2×10^{11} light years." You may not feel the error is quite so minor.

Let me turn now to large numbers in the genetic problem. I am told that nowadays a mutation with a frequency of about 10^{-9} can be detected. This obviously requires an awfully large number of Petri dishes. I am also told that Prof. Glazer of Berkeley, who is a proponent of large scale production—any of you who have seen any of his bubble chambers know what I mean—decided to have prepared a sheet of film covered with agar, about 2 feet in width and say 500 yards long. What did that mean in terms of increasing the likelihood of picking out a mutation of a frequency lower than 10^{-9}? Presumably, he can go now to approximately 10^{-11} or 10^{-12}.

Consider now something that may indeed happen and probably has happened in nature, the independent occurrence of three mutations, roughly speaking, 10^{-14} to 10^{-16}. Such a mutation is clearly completely inaccessible by such a technique. It is inaccessible at any time in the future unless you presumably agar-plate a great part of the surface of the earth. In other words, one must make a very clear distinction between the orders of order of magnitude. The numbers that I talked about and which relate to the diagrams that Professor Schutzenberger put on the board are of this inaccessible magnitude. We do not know the size of acceptable protein sequences. We can easily make an estimate of all thinkable protein sequences, and within this space it seems to me that the set of workable protein sequences is so minuscule as to be undetectable.

The Chairman, DR. WADDINGTON: But the point I wanted to make is that a lot of the thinkable protein sequences are inaccessible to life on earth. We can change a protein sequence by changing one amino acid at a time, or we could change it by a reading frame shift, which would make a coordinated change; but a lot of sequences way out in the other part of this space, we have no way of getting to. They are therefore irrelevant to our consideration. What we are considering, it seems to me, is only the part of the protein space that is contiguous to the part we are using.

DR. EDEN: This pre-biological mechanism had to find the small subspace in the first place, unless you assume that the space is uniformly accessible to life, although such forms may be completely different from what exists on earth. It poses the problem in a different frame, but we hang from the horns of the same dilemma. We can say that life could have originated almost anywhere in this space and it happened to have originated here; or else we are faced with the problem of explaining how life found that particular locus in space in the first place?

The Chairman, DR. WADDINGTON: I think your argument leads to the assumption that over most of the protein space there are proteins that are usable in some way for life; or, at any rate, in quite a large fraction of the space, and by chance we picked on one of them. If the fraction of usable proteins in the total protein space is small, then the chance that anything would ever have found it would be almost infinitesimal. We have to reject this assumption and say quite a lot of them have never been used.

DR. LEWONTIN: I disagree. Let me ask you this question: What is the probability that any individual will be precisely X centimeters tall? You may carry out X to as many decimal places as you like, and you know that the answer is, "Vanishingly

small." Nevertheless, every individual has some height in the continuum; and I think the fundamental metaphysical error which is being made here is to say that if the set of acceptable possibilities has a measure close to zero, relative to the measure of the entire space, life would never have arisen.

That seems to me to be a misuse of an inferential principle. The fact is that the event occurred, and it may have been a tremendously improbable event—an event with such a small measure as to have essentially the probability of zero. Nevertheless, every event which occurs in the universe has a probability of measure zero and every event does occur. I find it not interesting to discuss the question of whether the original event may have occurred. On the contrary, what is interesting is to discuss the question you have discussed; namely, given an initial condition, what is the size of the neighborhood in which that condition can spread out?

DR. WEISSKOPF: I don't want to defend quantum mechanics; neither do I want to defend Newtonian mechanics, but there is a question here. If you compare a physical theory with the situation as you have described it in evolution, there is a matter of measure—how big is the measure of what you can explain really well and what you cannot explain.

I have the following subjective feeling. Let us compare, for example, the quantum mechanics of atoms and the quantum mechanics of nuclei. In the quantum mechanics of atoms, we do believe we know the principle. It is the attraction of electrons by the nuclei and the wave functions of electrons developing under these conditions. In the quantum mechanics of nuclei we are not sure of the "principle"; we don't know too well what keeps the nucleus together. The experiments and theories are developed in nuclear physics in order to test our present ideas regarding the principle. We may find something completely unexpected which has escaped our notice; whereas in atomic physics we are pretty sure we will never link something that doesn't fit into the theory. I feel that the situation in evolution is rather to be compared with the situation in nuclear physics where we would like to look at it from all sides, because there is some suspicion that an essential point is still missing.

The Chairman, DR. WADDINGTON: I would agree with you to a large extent in connection with the mathematical formulations of neo-Darwinism—and here I am talking about neo-Darwinism rather than Darwinism. Really, they have changed the meaning of all the words and have left out a number of things which we know ought to be included in a general theory of evolution. Before we start looking for quite new, previously unsuspected essential points, I think we should examine the importance of these known but neglected notions. One thing left out of mathematical neo-Darwinism is something whose absence is very noticeable to me because it is my own subject—namely embryology. Another omitted point is the fact that a phenotype may largely determine the nature of the selection pressure that will be exerted against it. A new mutation may, for instance, produce an organism which to some extent insulates itself against competition with the rest of its species by utilizing different food-stuffs or by going and living in a different place.

DR. WEISSKOPF: If I wanted to be nasty toward the evolutionists, I would say that they are surer of themselves than we nuclear physicists are—and that's quite a lot.

Another point is, as you said at the beginning, there might be a mechanism in life that restricts the possibilities of proteins to an extremely small part of the configuration space. What is this mechanism? One mechanism, of course, is Darwinian evolution. Perhaps there are also other mechanisms. Could it be that certain proteins are just physico-chemically favored? The things that Sidney Fox told us are examples. I cannot judge the importance of his findings, but his results have impressed me as indicating an interesting possibility. It may be wrong to look for evolutionary restrictions of proteins only. Perhaps there were already some physical restrictions at the beginning.

The Chairman, DR. WADDINGTON: It seems to be most probable that different amino acid sequences have different inherent stabilities, but I don't know whether this would limit their use in life. In some of the living functions, it is probably desirable to have it be unstable.

You may be able to use the unstable protein species for some very good purpose, for instance, in processes like muscular contraction or nerve conduction.

DR. SHAHN: I would like to throw another example into the analogy hopper which I think is somewhat different in kind, again relating to physics. For many years the problems of extremely low temperature remained quite a mystery, the phenomena of superconductivity and superfluidity. The explanations as they evolved roughly a dozen years ago, seemed to indicate that there wasn't really a new fundamental force involved but, rather, that there was a cooperative behavior which has escaped analysis. This required a very difficult analysis before it finally yielded a result which, in some sense, from first principles, then agreed with the experiment.

This is not, I think, the same as the problems that Dr. Weisskopf has mentioned in nuclear physics, where it is thought that there are new forces involved. It is a different kind, and perhaps it is at this level that the mathematical analysis which will yield a solution to the evolutionary problems will evolve.

DR. FOX: We have been talking about the accessibility of protein sequences which are very minute fractions of what can be placed in conceptual space, and the context of this thought has nearly always, or always, been in the sense of internally restrictive forces which haven't been identified fully. I believe a second kind of explanation deserves to be entertained. Although we look back on what we regard as a long period of evolution, 2 billion years, this is in a sense a very short period of evolution; the natural experiments which comprise evolution are minute fractions of the experiments that conceptually might have gone on spontaneously.

From the point of view provided by protein molecules, evolution has been sluggishly slow. The explanation alternative to the one of internal restrictions (steric hindrance at the molecular level) is that variations in molecules simply have not gone far in a paltry two billion years (paltry as contrasted to the time necessary for an approach to a theoretically possible number of protein isomers). The kinds of protein molecules that have arisen are primarily determined by the most easily formed and fixed amino acid residue sequences rather than internally selected over sterically prohibited sequences.

DR. JACK SCHULTZ: It seems to me that in the terms in which you discuss the physical chemistry of the amino acid sequences, you are using a different language from the evolutionist. From the evolutionary point of view, the physical-chemical factors constitute the basis for selective advantages for particular amino acid sequences; thus we create difficulties if we set these factors in a category different from others in the selective process.

DR. WEISSKOPF: But the point is this: As Lewontin and so many others said, natural selection selects the least bad solution. The many possibilities are restricted to a few. What we are groping for is to understand how life started, so to speak, with the few that were selected. It is quite right that the physico-chemistry of an amino acid has nothing to do with the fitness; that is an accident.

DR. SCHULTZ: No, I would say it is part of the total fitness, eventually.

DR. WEISSKOPF: Eventually and philosophically it is part of the fitness, but it is not a naturally selected fitness.

The Chairman, DR. WADDINGTON: It would seem to me, intuitively, that these physico-chemical considerations are not likely to lead to profound insights. If a life process, much as a certain enzymatic function, demanded a special site that existed on a protein molecule that was rather unstable, I believe biochemical evolution would have found some way of stabilizing it. Why do so many enzymes have heavy metal atoms in them, and why does hemoglobin have iron in it? Presumably these are needed for stabilizing a sequence, for stabilizing a conformation of the enzyme, the active surface of the molecule. I believe that physico-chemical instabilities may be of minor importance, but life would have got around them if it wanted to.

DR. RALPH O. ERICKSON: It just occurs to me that L. J. Henderson, in his book on fitness of the environment, began a discussion of the sort of question that you have

raised. I don't know this very well, but I understand that he discussed at some length the particular appropriateness of water as a solvent and of iron as a component of oxidative enzymes, for example. But this subject hasn't been carried very far.

DR. SCHULTZ: On this question of Henderson's "Fitness of the Environment," I just want to recall an old anecdote that is not without an immediate relevance. Jacques Loeb, at the time the book was first published, was asked about it, and he said that this reminded him of a question that his then small son, Leonard, asked him, "Papa, why is it that big rivers always go by big cities?"

DR. EISELEY: I believe that Dr. Mayr mentioned this matter of the eye as controversial. I would like to point out simply for the sake of the record that I mentioned this in my introduction as representing an aspect of the matters we are considering. No one knows better than I that you can get different things out of Darwin. But one of the interesting things about that comment is that it was made before he had been subjected to quite the battering from critics which took place later on in the history of the "Origin." It occurred to me that it might have its uses in terms of emphasizing the problems of this symposium since Darwin had expressed concern about the complexity of this structure. The eye illustrated to Darwin's mind "mysterious correlations", something which the experimental biologist is still concerned with in connection with the different ways that an eye can be produced.

From this standpoint, I think Darwin was revealing his concern about the very thing we have discussed here. That is the whole problem of what randomness is, or what we mean by it, and the role that it has played in this situation.

Before leaving, since I did introduce this symposium, I would like to comment from another discipline because I think hopefully it may have some pertinence here. In the twenties and thirties, when the whole subject of early man in the United States was being debated and re-examined, the geologists and the archeologists were very much at loggerheads with each other. I can recall meetings in which, at first, they did not speak each other's language very well. There was considerable contention and indeed exacerbation over problems which in some degree represented differences of approach and vocabulary. But by degrees, as those meetings went on and the men of these separate disciplines began to speak each other's language and to understand each other's problems, something came out of this, some meeting of minds in both directions. Hopefully I would think that if symposia of this kind could be continued, similar helpful compromises in connection with the mathematics of evolution might emerge.

The Chairman, DR. WADDINGTON: I think with those remarks we really have come to the end of our allotted time and I hope nobody wants to throw up some other major philosophical problem, as it were, between the biologists and the physicists. I think we have approached each other to some extent. I hope the biologists have shown the physicists that evolutionary theories are not totally vacuous. I think the physicists have shown us that they are certainly as yet very incomplete, and I think we are ready to realize they are very incomplete. Possibly we now know slightly better in which directions they are incomplete.

The people who will get any practical benefit out of this conference, I suppose, are the biologists. It is unlikely that the physicists expect to go home and reformulate their problems to themselves; but the biologists are here to learn and I think have learned something, possibly even quite a good yield for 36 hours or whatever it is that we have spent on it.

I should like, on behalf of all the visitors here, first to thank the Institute and the arrangers very much indeed for arranging this symposium. I don't think I need to say much more than that since the liveliness of the discussion has shown that the people you gathered here certainly had a lot to say to one another.

DR. PAUL S. MOORHEAD: Thank you very much, Dr. Waddington. I just want to thank all the participants, on behalf of The Wistar Symposium Committee, and to speak for the non-combatant biologists, that we did indeed profit very much.

Some Ecobehavioral Problems to Mathematical Analysis of Evolution

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I can see many problems that will have to be overcome before any completely acceptable mathematical model of evolutionary concepts can be developed. As a vertebrate ecologist, I want to point out just a few of the prodigious number of ecobehavioral postulates, some of which fortunately do have an empirical basis, that complicate any completely satisfactory mathematical analysis of evolution at this time. Just because there is insufficient biological knowledge at the moment to suitably integrate these many phenomena, however, does not mean that these are inauthentic phenomena. I cannot accept the mathematical arguments of M. Eden and M. P. Schutzenberger that many of the statements of the principles of evolution are tautologous. Evolutionary theory, at least to me, is certainly not vacuous.

Before I discuss the interaction of behavior and ecology to evolutionary processes, I have a few other comments which stem from this stimulating symposium. One is that many of the oral discussants, because of an inherent weakness in verbal communications, too frequently and inadvertently tended to infer that any change in gene frequency is *ipso facto* an example of speciation, whereas this usually is not so. All changes in gene frequency are not necessarily evolutionary entities along a one-way street; gene combinations may ebb and flow as a population adapts and readapts to changes in the environment by natural selection of the variations in the properties of phenotypes. Another common confusion in oral discussions of evolution, which was prevalent at this symposium, is the attempt to debate simultaneously both the principles of speciation and the origin of life. This produced a dichotomy of views which in reality I do not think actually existed in the minds of the participants.

I will use vertebrates to illustrate some of the ecobehavioral problems I foresee that will prevent adequate mathematical modeling of various phases of evolution in the near future. I have expressed many of these views more fully elsewhere (1).

If mammals are to be selected as subjects for mathematical modeling of the mode of action of the principal variables affecting intraspecific genetic differentiation in adaptive responses of populations, that for one reason or another have been emancipated completely from their parental gene pool, several real problems appear. The genetic differentiation of mammals is based on recombination of polymeric genes; mammals have few oligogenic characters or at least they are difficult to identify. They do not have the convenient meristic variation in characters that occurs in scales, fin rays, etc., of fish, except over geologic time. Polyploidy is not common. However, currently, with a National Science Foundation grant we are finding a number of polymorphic differences in the serum and hemoglobin of rodents by means of starch-gel electrophoresis, which permits a qualitative separation of serum proteins into specific electrophoretic "zones" in specially prepared starch-gel beds. With this method we hope to be able to record certain changes in gene frequencies of wild rodent populations separated either spacially or temporally, as the result of acclimatization to modified environments. In conjunction with these studies, we are also utilizing a Public Health Service grant to evaluate the genetic parameters of the olfactory acuity of rodents and

the propensities of rodents to develop bait and toxicant shyness; but even these techniques will not necessarily enable us to discover any final proof of speciation in mammals that will be helpful to the mathematicized analysis of evolution. I do not think we will be forced to wait for astronauts to bring us genetic material from other planets, although this will be helpful.

The mechanisms distinguishing a mammal's genotypical makeup from its phenotypical expressions in the field of behavior must be prodigious. It is likely that not only are many genes and modifiers involved, but that the variables of physiochemical influences, environment, instincts, ontogeny, and learning further confuse the phenotypic responses in behavior. With wild mammals it is often difficult to differentiate between genetic phenotypes and the more subtle alterations which are merely the consequence of diet, weather, latitude, disease, or social factors. Similar phenotypic effects may be the consequence of different multiple gene combinations acting under various environmental conditions.

The ecosystem is the basic unit of structure and function that evolutionary models must ultimately deal with, but it is kaleidoscopic in nature and such changing scenes and patterns are not easy to deal with. I do see merit in setting up conceptual models from those constituent parts that are explicable in physiochemical or ecobehavioral terms, in hopes that their combination will imitate or reproduce the properties of the whole component. However, it is often difficult to test the validity of conceptual models concerned with the ecology and behavior of vertebrate populations, even when the performance of the model appears identical to that of the actual biological system, because of the danger of analogy of other and obscure mechanisms having the same relationship between input and output. Nevertheless, even though the relationship between stimulus and response in the behavior of vertebrates is dynamic and highly complicated, the existing knowledge of the parts should be carefully scrutinized mathematically, and then attempts made to resynthesize this information into appropriate evolutionary concepts.

With this introduction, I will cite briefly several examples of ecobehavioral phenomena of vertebrates to illustrate the complexity of integrating such concepts into mathematical models of speciation. A principal factor governing distribution and density of mammal populations is the suitability of the respective habitats—that combination of vegetation, soil and other environmental factors which enables various species of wildlife to live in a particular locality. It has been my observation that a wildlife habitat which has evolved over long periods of time undisturbed by man, and which is composed only of native plants and native animals, creates a well-established, stable, soil-vegetation-complex which is *not* delicately balanced. Natural changes (e.g. by disease) or man-caused changes (e.g. by shooting) in the density of any one of the native species of browsing, grazing, seed-eating, or predatory vertebrates may affect the balance of nature in a natural community. However, such changes usually do not precipitate a dramatic chain reaction of responses by the other components of the community, unless there are associated significant disturbances of the vegetation-soil complex. Stable, balanced biomes become disrupted and then precipitate marked chain reactions usually as the consequence of some human disturbance such as the introduction of alien species of plants or animals, farming, grazing, logging, or use of fire.

The irregular pattern of success and failure of vertebrate introductions throughout the world indicates that most local biotas have vacant niches that certain organisms, which evolved elsewhere, can often successfully colonize. Vertebrates are acclimatized often without any apparent reduction in the densities of other species of vertebrates. The wider the tolerance of a new arrival, the greater will be the number of new but suitable niches available to insure its survival, without any immediate genetic differentiation, especially of evolutionary significance, being required.

Animal populations have considerable powers of self-limitation (compensatory mortality, decreased reproduction, and/or increased dispersals) which prevent severe overpopulations that otherwise would de-

stroy the species. Self-limitation counteracts the innate ability of vertebrates to produce a surplus of offspring. A species automatically adjusts its density in different places, and in the same place at different times, in relation to the prevailing environmental conditions; and it maintains a state of stability under all conditions which are not inherently intolerable. This mechanism may enable populations to remain in being in spite of great changes in the environment, without any necessity for the development of new adaptations. But, surely, as a result of mutations, subtle adaptive genetic changes, which are irreversible and lead to a loss of cross-fertility, would occur under these circumstances; and these are what we need to learn how to measure in vertebrates.

Members of a species become their own brake to counteract their great reproductive potential, although the upper density limits may be raised or lowered whenever man modifies the environment. Self-limitation mechanisms stop mammals from multiplying beyond certain ill-defined maximum density limits before they have destroyed all of their food resources. Individual mammals often starve to death, die of disease, or are killed by storms, but populations of wild mammals do not exhaust all the food within a sizeable area, with the result that all who live there then die. Similarly, if they are provided with ample cover and all the food they can eat, they still do not continue to multiply up to the point where they form a solid mass. In fact, with surplus food, they do not even become much more numerous, relative to the theoretical limits, than they are in other localities where habitat conditions are favorable. The growth in density of all vertebrate populations stops when a certain inherent equilibrium density is reached, and it is at this level of density that the various self-limiting forces become effective. Just how these complex controls operate is not understood. The phenomenon is probably Nature's way of preserving the species, with these various mechanisms having evolved over long periods of time through natural selection.

A few remarks regarding the complexity of analyzing interspecific relationships of vertebrates will provide another illustration of the difficulty of designing suitable mathematical models. Vertebrate predators, I have observed, usually do more to perpetuate a greater, not lesser, seasonal and annual density of their prey. Densities of vertebrate populations are determined primarily by the suitability of the habitat and self-limitation due to intraspecific stress factors (psychological, competition for food or mates, territoriality, weather, disease, or other vicissitudes of life); whereas interspecific competition, especially the interactions of predator and prey, often is only of relatively minor significance. "Self-limitation" may come into play at lower density levels in the absence of predation, but when the demographic structure of the population has been materially altered by predation, self-limiting factors lose some of their stabilizing influence in regulating populations at the lower levels of density.

I believe enough has been said to illustrate the complexity of the problems we face. Until ecologists can obtain a keener insight into the factors that regulate productivity and stability of vertebrate communities, it is difficult to obtain the needed empirical evidence about the processes of speciation. But there is need for greater leadership in mathematical approaches that will suggest hypotheses, which the biologist and geneticist can then attempt to confirm. It appears to me that much of the essential logic of evolutionary theory will be determined in the future from new concepts about the complex biological entities involved and their delineation as entities, not from the quantification of biological measurements.

The great complexity of most ecosystems, and how they affect gene flow, largely prevents elegant explanatory constructs for the time being. This restricts effective use of sophisticated computerized language because any theoretical formulation or model should have one or more testable field consequences, which is not always easily done with evolutionary concepts. Also, unfortunately, sometimes statistical analyses of research data can make an apparently paradoxical set of measurements of observations intuitively acceptable.

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Comments on Mathematical Challenges to the Neo-Darwinian Concept of Evolution

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A major feature in understanding the evolution of adaptive form and function is the realization that this is essentially based on the survival of the least inadequate. A successful species is not one which is adapted to a particular environment but rather one which is least badly adapted to that environment. Evolution is based, not on superlatives, but on adequacies. This can result over a long time period in the construction of remarkably complex structures which appear to confer a superlative adaptation to the environment.

There is, then, a naive tendency to refer the processes of evolution to these end-points, arguing that such complex structures cannot have evolved on the basis of a genetic system of random mutation. If, however, the genetic basis for such "end-points" of evolution is examined, then it is almost axiomatic that a single genetic combination is not involved. The genotype for any character consists of a melange of variation which has been constrained in various ways to result usually in the adaptive norm. In sexually reproducing organisms any specific haploid combination of the genotype is usually unfit as a homozygous diploid, yet junctions of separate haploid combinations have an adequate survival. Individuals are heterozygous for recessive lethal or semi-lethal genes at many loci. This genetic inadequacy is manifest only in homozygotes; the "normal" individual is maintained in its normality by the actions of the normal alleles to these recessive lethals.

The same type of phenomenon can be seen at the intragenic level. Separate mutations of the same gene which are each lethal as homozygotes may interact to produce a normal function. It would appear that each mutation produces a protein product which is defective, but the polymerization of the two differently defective proteins can result in an effective unit. It would appear logical for the evolution of some adaptation to result in the fixation of one particular genotype, but this appears only rarely to have been the case. The more frequent result is that evolution has resulted in the construction of constraints of the expression of genetic variability. This apparently inefficient and illogical result is based on the need to maintain a compromise between the immediate benefits of stability and the long term values of variability. Sexual reproduction with its concomitants of genetic combination and recombination, results in a myriad of genotypes. Constraints on the expression of this variation lead to immediate adaptations without reducing more than slightly the multi-dimensionality of the genetic system.

Combinations of different genes occur such that every individual is a unique combination, and the selective assay of the value of each random mutation is performed simultaneously in this framework for thousands of mutations at a time. The acceptance of the neo-Darwinian concept of evolution appears to be eminently valid on this basis. However, a critical feature is the occurrence of mechanisms for genetic combination and recombination, and a major criticism of the neo-Darwinian concept which has been raised at this meeting is premised on the lack of such a mechanism in the initial steps of the evolution of a "sense" sequence of a polypeptide or polynucleotide from an initially "nonsense" sequence. It does not, however, seem an extreme extrapolation from the known facts of nucleic acid replication and transcription to envisage that combination and recombination are inherent features of polynucleotides, and the evolution of "sense" sequences then becomes a process of reasonable probability.

Inadequacies of Neo-Darwinian Evolution as a Scientific Theory

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During the course of development of neo-Darwinian evolution as a theory, a variety of suggested universal postulates with empirical content have been invalidated. For example, the postulate that environmental influences on parents cannot affect offspring was invalidated by the discovery of induced mutations. In like manner, the notions that genes alone govern inheritance or that no morphological changes in a phenotype will propagate in its descendants have also been experimentally contradicted. In consequence the theory has been modified to the point that virtually every formulation of the principles of evolution is a tautology.

As an instance, the statement that species adapt to changes in an environment by a variation in the properties of phenotypes and by the consequent process of natural selection is clearly vacuous. If a strain of some species, say a plant, is placed in some new environment, either it will die out or survive, generally in a morphologically modified form. If the seeds are eventually returned to the original environment and are observed to have morphology that phenotypes exhibited in that environment originally, then this is taken as evidence that all or some of the individuals of the strain could adapt in either environment. If, on the other hand, the seeds returned to the original environment maintain the morphology of their immediate parents, then it is adduced that some heritable adaptation has been made and further hereditary readaptation is required if the strain is to survive. Since these are the only possibilities, the original statement is tautologous.

Modern biology has identified the mechanism of heredity with the genes and in particular with the linear DNA chains (except perhaps for cases in which cytoplasmic inheritance needs to be included as an additional factor). There is every reason to believe that different species have differences in the DNA sequences which comprise their chromosomes. Hence, it is at first sight plausible to propose that speciation and indeed the whole panorama of the origin of life proceeded by a chain of small mutations and rearrangements in the apparatus of inheritance and that the resulting phenotypes most suited to the environment survive best. However, it is also assumed that these genetic variations are undirected.

Aside from the pre-Darwinian postulate that offspring resemble their parents, only one major tenet of neo-Darwinian evolution can be said to retain empirical content; namely, that offspring vary from parental types in a *random* way. It is our contention that if "random" is given a serious and crucial interpretation from a probabilistic point of view, the randomness postulate is highly implausible and that an adequate scientific theory of evolution must await the discovery and elucidation of new natural laws—physical, physico-chemical and biological. Until such time, neo-Darwinian evolution is a restatement in current terminology of Darwin's seminal insight that the origin of species can have a naturalistic explanation.

A. The complexity argument of "There is not nearly enough time available."

A number of specific arguments may be given; only two will be sketched here.

i. Since multicellular organisms develop in quite specific ways, it is assumed that to each organism there is associated an algo-

rithm in some finite alphabet for the production of the phenotype within some expected range of environments. For the sake of concreteness we may think of the linear DNA chain as embodying the algorithm and that the algorithm prescribes the orderly formation of specific polypeptide chains. Clearly to every ancestor of an organism living today there is associated a meaningful DNA sequence. In humans the linear DNA sequence is estimated to contain on the order of 10^9 nucleotides. Taking the length of time life has existed on earth to be of the order of 1 billion years, we find that the average rate of accretion is about one meaningful nucleotide to the DNA sequence per year. If randomness is taken to mean that a uniform probability is assigned to each possible independent substitution or addition, the chance of emergence of man is like the probability of typing at random a meaningful library of one thousand volumes using the following procedure: Begin with a meaningful phrase, retype it with a few mistakes, make it longer by adding letters, and rearrange subsequences in the string of letters; then examine the result to see if the new phrase is meaningful. Repeat this process until the library is complete.

ii. Current biological theory suggests strongly that the products of the genetic apparatus are in the first instance meaningful, i.e., functioning proteins. Now the space of all polypeptide sequences of length 250 or less contains about 10^{350} members. Over the last billion years a very liberal estimate of the number of genetic couplings is about 10^{37}. In fact the number of protein molecules of such size that ever existed on earth can be estimated to be less than 10^{55}. Thus, either the vast proportion of polypeptide chains perform useful biological functions in some integrated entity (a rather implausible hypothesis) or else evolution was directed to the incredibly small proportion of useful protein forms (by environmental constraints? by thermodynamics?, by some as yet unexplored physical relation?).

B. The thermodynamic argument of "There is too much time to explain away."

Those processes related to the development of organisms whose kinetics and equilibria have been studied are uniformly characterized by a very high likelihood for the existing biologically useful form and by a very rapid time course. Examples are: the formation of amino acids from the reaction of simple gases produced by non-specific energy sources (1-3), the helical configuration of either polypeptides or nucleotide chains as well as the tertiary structure of biologically active proteins when placed in aqueous media of appropriate ionic strength, the recombination of synchronous DNA chains in melting-freezing cycles (4), the reconstitution of collagen fibrils exhibiting complicated long-range periodicity (5), the spontaneous formation of muscle fibrils from myosin solution. Note, too, that in processes of micro-evolution a very small selection bias will change the character of a population in a very few generations (order of magnitude 40).

No processes which appear to be relevant are known that involve events of such low probability that the time course to some new level of stability has time constants of the order of 10^4 to 10^6 years. The only such processes which have been empirically observed and for which mechanisms can be postulated are either cosmological or geological events. Unless a specific mechanism and probabilistic structure is proposed, the postulation of events which occur on an average of every 10,000 or 1,000,000 years is plausible only in the vacuous sense that we know about a billion years ago life appeared on earth and that some account must be given for the fact that it has taken this length of time to reach the current stage of evolutionary development. Aside from its usefulness in formulating certain problems of evolution, it adds nothing to the validity of the theory.

In summary, it is our contention that the principal task of the evolutionist is to discover and examine mechanisms which constrain the variation of phenotypes to a very small class and to relegate the notion of randomness to a minor and non-crucial

role. In terms of the library analogy mentioned above, the discovery of the syntactic and semantic rules of the genetic language are the pertinent tasks; a knowledge of the workings of the typewriter may be interesting but will probably furnish little information about the language. Another analogy may be found in chemistry: it is accepted that the law of mass action is derivable from the assumption of random collisions between reactive molecules, but the explanation of a chemical reaction in which molecules A and B become C is to be sought in a study of the relation between molecular structure and reactivity and not in a random rearrangement of the atoms of A and B.

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The Principle of Archetypes in Evolution

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Classical neo-Darwinian theory may be summarized as a system which involves:

a) Random gene mutation, treated as a repetitive process so that each mutational change can be assigned a definite frequency.

b) Selection by "Malthusian parameters," i.e. effective reproduction rates.

c) An environment which is treated as uniform, that is, it can be neglected.

d) The phenotype has no importance other than as the channel by which selection gets at the genotype.

This system is theoretically a closed one, which does not lead to continued evolution, but at best to a passage leading to a state of equilibrium. The possibility of continued evolution requires the postulation of one or more of the following additional points:

1. A continued change in the environment, arising independently of the existence of the organisms within it.

2. An initially heterogeneous environment, whose heterogeneity is continually increased by the fact that different populations evolve into adaptation to the initial sub-environments; i.e., the organisms adapted to other environments form part—a changing part—of the environment of the organisms in the sub-environment under consideration.

3. The existence of epigenetic organization of the phenotype, so that the phenotypic (i.e. selectional) effect of a gene mutation is changed when it occurs in a later-evolved organism from what it had been at an earlier stage.

4. The possibility of the occurrence, at later stages, of types of gene mutation which were theoretically impossible at earlier stages (e.g. the occurrence of an intra-genic duplication would then make possible types of mutation which previously could not occur).

It seems almost certain that all these factors have in fact played a part in evolution as it has actually occurred. The questions then to be asked are: How have they operated so as to result in the appearance of only a restricted number of different types of organisms? Why are there no organisms which simultaneously exploit the full potentialities of myosin (active movement) and chlorophyll (photosynthesis)? Why are there no vertebrates as thoroughly hermaphroditic as some molluscs? In other words, once you have got a theory which makes continued evolution possible the major problem is to provide a general theory of phenotypes. Factors 1 and 4 above clearly do not provide any basis for limiting the freedom of phenotypic forms. The choice lies between factors 2 and 3; and it seems doubtful whether the types of environment (i.e. of selective pressure) which might arise (factor 2) could be shown to provide any principles of limitation. It therefore appears to me that the crucial issue is factor 3, i.e. the epigenetic organization of the processes by which the genotype becomes developed into the phenotype.

The main elements in the theory of phenotypes are:

a) "The canalization of development" (i.e. what is often crudely called "developmental homeostasis," *plus* switching mechanisms);

b) the heritability of developmental responses to environmental stimuli;

c) the theory of "archetypes."

Items a and b, taken together, produce, among other things, the process of "genetic assimilation"—the only radically new, experimentally verified, evolutionary process

discovered in the last twenty years (?). It is item c which I wish to discuss further.

The Principle of Archetypes in Evolution

Evolution is brought about by the natural selection of random variations which occur in the genetic material, which—in conjunction with environmental influences—determine the phenotypes of the organisms which have to find some way of earning a living in the natural world. The point towards which attention is being directed in this Note is the fact that the individuals on which natural selection operates are *organisms.* That is to say, their character is not a mere summation of a series of independent processes set going by a number of disconnected genetic factors, but is instead the resultant of the interaction (involving all sorts of feedback loops, mutual interference, mutual competition, etc.) of a number of elementary processes for which the individual genetic factors are responsible. Now a major characteristic of such interacting systems is the existence of "threshold phenomena." Suppose that we have an organized system subject to variation and natural selection makes the demand on it that a certain parameter should reach a minimum value p. It will very likely be the case that the first variation which attains this value p actually interlocks with the other elements in the organized system so that, in fact, it attains a value of p x n, where n may be quite a large number.

Consider an excessively simple case. Imagine in a two-dimensional universe an organism which was faced with the necessity to protect its internal contents against the random buffetings of the external world; the organism is to be thought of as having protective elements in the form of three rods of relatively rigid material joined together at the ends by joints around which movement is possible. Now if these three rods are such that the sum of the lengths of the two shorter elements is less than the length of the longer element, they can form a sort of protective arc whose strength can only be increased by increasing the friction at the terminal joints. This will give the whole configuration a certain, but quite restricted, resistance to deformation. If, however, the length of the two shorter arms is increased so that the whole system can join together to form a triangle, the overall resistance to deformation of the configuration suddenly leaps up by many orders of magnitude—probably by much more than existing circumstances were demanding of it.

I should like to suggest that a major factor in large-scale evolution has been this sort of "hitting-the-jackpot." For some relatively trivial local reasons certain arthropods, varying indefinitely over a whole range of phenotypes under the influence of natural selection, come up with a form involving three legs, two pairs of wings and respiration by tracheae. It turns out to their surprise (if a phylum can feel such a sentiment!) that this particular pattern of organization opens out the whole range of the insects. Another group comes up with an "archetype" of eight legs with no proper division between the head and the thorax, etc. and they find they can develop into the whole range of the Arachnida.

There should be—but unfortunately there are not yet—large chapters in the mathematical theory of evolution concerned with such questions as:

1. Under what circumstances does selection for a slight increase in a parameter X in an organized system lead to an increase in X by several orders of magnitude?

2. How can you distinguish between topologically distinct patterns of organization? Consider automobiles. There is the motor bicycle pattern, with one wheel to drive, one to steer and no lateral stability. There is next the three-wheeler, with either one to drive and two to steer or *vice versa,* and some lateral stability. There is the standard four-wheeler, usually with two to drive and two to steer, but possibly with both pairs driving and/or both pairs steering. Then there is the tractor vehicle, which amounts to an infinite number of driving units and I am not sure how many steering units. Is it conceivable that there could be a biological topology which would show why you can get large classes of animals with two, three or four pairs of limbs, or an indefinite number of pairs as in Myriopods, but there is no major class with six or seven pairs. Again,

you can get symmetries based on two, four, five, and six axes but not, apparently, on seven. Or is this perhaps merely a contingent accident that no animal phylum during evolution happens to have hit on a seven ray symmetry? But even without tackling the possibly insoluble problem of why evolution hasn't done what it hasn't done, we certainly cannot be content without some further understanding of how these small-scale processes of natural selection of minor variants in relation to immediate needs have produced a restricted number of basic "archetypes"—the protozoan, the annelid, the insect, the vertebrate—which are flexible enough to become adapted to almost any system of life yet have sufficient inherent stability to do so without losing their essential character.

3. The notion of an archetype, as described above, is really too "simpliciste"—for purposes of preliminary exposition. What we really have to do with always involves times, and in the context of evolution, involves it at two (or more) importantly different scales. In the first place, an archetypal form of individual organization (an insect, an arachnid, etc.) is not simply the conventionally accepted adult configuration—it is the whole epigenetic trajectory leading from the egg to the adult. It is an archetypal chreod.

Here it is worth noticing the difference between an archetypal and the usual kind of epigenetic chreod; both are "canalized" and protected by threshold-like barriers against disturbances; but in normal chreods the thresholds lie where they do only because natural selection has put them there, by selecting certain values of particular parameters. In an archetypal chreod on the other hand, the position of the thresholds is fixed by internal necessity. (Is this what René Thom calls "stabilité structurelle"?). You can't have a triangle unless $a + b > c$. Of course it is natural selection which picks out one archetypal chreod as something to be exploited, but it has not created it; whereas it has created the normal epigenetic chreod out of a situation in which no chreod is logically necessary.

To return to the main argument, an archetype should probably—I am not quite sure of this—be regarded as time-extended on the evolutionary time scale. You don't just get a "horse archetype," a "dipteran archetype," but you get a "horse family archetype," with inbuilt characteristics of directions in which evolutionary change can easily go.

Comments on the Preliminary Working Papers of Eden and Waddington[1]

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There is likely to be much discussion at cross purposes because of different concepts of what neo-Darwinism is. Therefore, I had better try to make clear what I understand by a Darwinian process by quoting the opening sentences of a recent paper (1).

"The idea that evolution comes about from the interaction of a stochastic and a directed process was the essence of Darwin's theory. The stochastic process that he invoked was the occurrence of small *random* variations which he supposed, provided the raw material for natural selection, a process *directed* by the requirements of the environment and one that builds up, step by step, changes that would be inconceivably improbable at a single step."

The meaning of "random" in this context is perhaps a source of some misunderstanding. All that is meant is that the variations are, as a group, not correlated with the course subsequently taken by evolution (which is determined by selection). The variations are, of course, severely limited in kind by the accumulated results of past evolution. Those that are seized upon by selection are ordinarily ones that are very slight phenotypically.

I have never heard of Eden's "universal postulate" that environmental influences cannot induce mutations. Even before Muller's discovery of induction by X-ray (2) it was presumed by geneticists that every mutation has an adequate immediate cause. The effects of systematic change in the amount of radiation to which organisms are exposed has been widely discussed by population geneticists (e.g. by Haldane and myself among alleged "classical neo-Darwinists") (3).

Population genetics is based on the evidence that hereditary differences are to an overwhelming extent Mendelian, but the reality of non-Mendelian difference (some plastid characters for example) is not questioned.

Natural selection may appear to be a vacuous and tautological principle if only a single step is considered, but considered over a long succession of little steps, it is the only guiding principle that has stood up under experiment. Eden refers to the 10^{350} proteins, each consisting of 250 amino acids. He seems to imply that it would require something like this number of operations of natural selection to arrive at a particular useful one. On the principle of the children's game of twenty questions in which it is possible to arrive at the correct one of about a million objects by a succession of 20 yes-or-no answers, it would require less than 1250 questions to arrive at a specified one of these proteins. While this is not a perfect analogy to natural selection, it is enormously more like natural selection than the typing at random of a library of 1,000 volumes with its infinitesimal chance of arriving at any sensible result.

Section B of Eden's document considers the opposite system: comparison of organic evolution with a practically completely deterministic chain of physico-chemical processes, such as is supposed to determine the "evolution" of a star. The Darwinian process of continued interplay of a random and a selective process is not intermediate between pure chance and pure determinism, but qualitatively utterly different from either in its consequences.

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"Neo-Darwinism" like the "synthetic theory of evolution" is an expression that is used in various senses. The phrase "classical neo-Darwinism", however, seems usually to refer to views developed in the 1920's and 1930's on the implications for evolution of studies on the statistical consequences of Mendelian heredity, made largely by Haldane, Fisher and myself. There is usually an implication that this constituted a single viewpoint. The mathematical results of analysis of a great variety of postulates did indeed form a consistent system but the choices as to which biological postulates were most significant in interpreting evolution were in some respects very different. Fisher, for example, rejected altogether the kinds of stochastic and directed processes that seemed to me most important (4).

Waddington's summary of the postulates of "classical neo-Darwinist theory" seems much too narrow to have satisfied even Fisher and does not include the ones that I emphasized most in 1929 and later. His proposed additional points were also used by all of us to varying extents but still are not sufficiently inclusive. What my main postulates were will be brought out later.

Whatever it is called, the aspect of evolutionary theory to which population genetics contributes should be carefully distinguished from other aspects to which it cannot contribute. It depends on the occurrence of Mendelian heredity, which depends on the existence of genes that duplicate with high precision and do so as of the new type, if by any accident an error in duplication has occurred. Furthermore, it depends on the assemblage of such genes in a cell capable of maintaining an adequate metabolic system, a cell with the mechanisms required for equational division, for conjugation, and a compensatory reduction division. All of this implies a long history. It is probable that the period of time from the origin of anything that could be called living to the appearance of fully equipped cells was longer than the period from that point to the present.

Presumably this pre-Mendelian evolution depended on the interplay of random processes at the chemical level and selection of systems for orderly molecular duplication, for mitosis and meiosis, as well as for metabolic adequacy; but we can only speculate on this phase since current living organisms all seem to have the same apparently arbitrary trinucleotide-amino acid code and thus to be of common origin. The specific propositions of population genetics obviously do not apply in this phase.

Evolution after the establishment of Mendelian heredity includes two phases: (1) that within species by which there is transformation into a new species and (2) the evolution of higher categories (genus to phylum). Population genetics applies directly only to the former since the latter does not involve crossing followed by Mendelian segregation and recombination.

Analysis of the speciation phase requires not only the abstract framework provided by mathematical population genetics but also the observations of field naturalists on actual population structures, on possible selective differences in nature, and on experimental studies of these.

The interpretation of macroevolution has consisted largely of the speculations of comparative anatomists and paleontologists. Waddington's theory of archetypes applies to this last phase. The point here is that interpretations of the three phases are in no sense alternatives, but are complementary in the interpretation of evolution as a whole.

Two radically different Darwinian processes have been postulated as occurring within species. In the more obvious one, mutation is the random process and mass selection is the directive process. In a given homogeneous population, mass selection can operate only according to the average differential effects of alleles. There can be no selection among interaction systems. This is a fairly obvious consequence of meiosis, but was demonstrated by Fisher (4) in his "fundamental theorem of natural selection". I doubted the adequacy of this process by itself, in my first paper (5) on evolution in nature, an abstract of a paper that came out in 1931.

"In too large a freely interbreeding population there is great variability but such a close approach of all gene frequencies to equilibrium that there is no evolution

under static conditions." This is much what Waddington writes. I recognized that this was somewhat too strong a statement in 1931 and instead of "no evolution" wrote:

"With an unlimited chain of possible gene transformations, new favorable mutations should arise from time to time and gradually displace the hitherto more favored genes but with the most extreme slowness even in terms of geologic time."

This was under the assumption of static conditions. I went on to point out that under changed conditions there would be relatively rapid readjustment on the basis of hitherto slightly unfavorable alleles, now the most favorable, that had been maintained in the species by opposed pressures. In this paper I considered such changes to be too easily reversible to be of much long-run significance. In 1932, however, I recognized that because of the inevitability of a vast number of selective peaks in the multidimensional "surface" of selective values of total genotypes, the process would actually be practically irreversible, and would constitute an "important evolutionary process." This has continued to be my view and is that to which Haldane's and Fisher's theories apply best (3, 4, 6, 7).

I have not, however, considered it to be as important for the evolution of a species as a whole as an entirely different Darwinian process that I advanced in 1929. In the 1931 paper, I introduced the topic "selection pressure" with the statement:

"Selection whether in mortality, mating or fecundity applies to the organism as a whole and thus to the effects of the entire gene system rather than to single genes. A gene which is more favorable than its allelomorph in one combination may be less favorable in another. Even in the case of cumulative effects, there is generally an optimum grade of development of the character and a plus gene will be favorably selected in combinations under the optimum but selected against in combinations above the optimum."

With respect to mutation, I stated:

"The foregoing discussion has dealt formally only with pairs of allelomorphs, a wholly inadequate basis for consideration of the evolutionary process, unless extension can me made to multiple allelomorphs . . . each gene has a history which is not mere oscillation between approximate fixation of two conditions but a real evolutionary process in its internal structure. Presumably, any particular gene of such an indefinitely extended series can arise at a step from only a few of the others and in turn mutate to only a few. Since genes as a general rule have multiple effects, a change in one effect need not involve others. It is probable that in time a gene may come to produce its major effects on wholly different characters than at first."

I would replace "few" by "several thousand" now. A chain of 1,000 nucleotides could give rise to 3,000 mutations each by a single replacement, about 4.5×10^6 at two steps and 4^{1000} altogether. In a population as large as the human species, 3×10^9, a mutation rate of 10^5 at each locus implies that all single step mutations from the common alleles will recur in every generation. Even the presence of only ten reasonably common alleles at each of only 100 loci implies more potential kinds of genotypes than there are elementary particles in the known universe. It is safe to say that, excluding identical twins, no two human beings or two members of any reasonably large species have ever had the same genotype.

As noted earlier, factor interaction implies that the "surface" of selective values in the multidimensional field of gene frequencies must have innumerable peaks. Mass selection holds the population to one under static conditions. It leads to evolutionary change in the changing field brought about by changing condition, but this should be much less effective than a form of selection according to the genetic system as a whole, if this is possible.

The process that I have considered most important is that in which there is fine scaled subdivision, at least in parts of the range of the species in question, such that local populations are sufficiently isolated to permit some degree of genetic differentiation but not so isolated as to prevent excess diffusion from the better adapted ones. In my 1931 paper, I dealt mathematically only with completely random differentiation due to accidents of sampling in populations that

are either small or that go through bottlenecks of small size (as in the founding of colonies.) More generally, however, local differentiation depends on the whole history of the population with respect to differences from others in conditions of selection, immigration, mutation, etc. It is merely required that there be an extensive differentiation that is random with respect to the subsequent course of evolution, not necessarily random in any absolute sense.

Whatever its nature, local differentiation and intergroup selection (by excess population growth and diffusion from the better adapted centers) form a coupled Darwinian pair of processes that should be more effective for evolution of the species as a whole than the pair—mutation and mass selection—whether conditions are static or changing.

There is abundant evidence for local genetic differentiation. It is obvious in the human species, in which it is also obvious that a considerable change in average genetic composition has come about in the last 5000 years by expansion of the genetic influence of some populations, contraction of others.

Evolution in a homogeneous population by mutation and selection is limited in a static environment by the exceedingly low rate of occurrence of novel favorable mutations. It is not so limited under changing conditions since genes that have been unfavorable may become favorable on the average. It is limited however, by the absence of selection among genotypes as wholes. This limitation is removed in a subdivided population in which local differentiation and differential growth and diffusion constitute the dominating basis for evolution. The actual limiting factor may either be so much diffusion that local differentiation is impossible, or the absence of conditions for differentiation, even under isolation. There is the possibility, however, of an indefinitely great number of evolutionary steps without the occurrence of any mutation that would be considered favorable in itself.

With respect to the long term aspects of the evolution of higher categories, the stochastic process is speciation. This was treated as *directed* above but may be essentially *random* with respect to the subsequent course of macro-evolution. The directing process here is selection between competing species often belonging to different higher categories. I have given my views on this process in an article on Evolution in the Encyclopaedia Britannica (8). As noted earlier, this is the phase to which Waddington's theory of archetypes pertains.

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Algorithms and the Neo-Darwinian Theory of Evolution

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According to the "dogma" the whole of genetic information should consist of a rather limited set of words in an alphabet of 20-odd letters. Then the only evolutive mechanisms which are ever mentioned are what might be called "typographic changes," i.e., suppression, duplication, transposition, and substitution of letters or blocks of letters, subject to short-range and eventually periodic constraints. Thus there is a striking similarity between these assumed blueprints of living organisms and the formal systems which underlie both programming languages and the simplest non-trivial models of natural ones. It must be emphasized that this framework implies an extremely special net of proximity (of derivability) relations on the set of all words considered. This we may call the "syntactic topology."

From another point of view, organisms are related by another topology which simply results from their being physical objects in space-time. Although this second topology is far harder to formalize, it is the basis of systematics, and it is objectively studied when observing the developmental effects of variations in the milieu. We call it "phenotypic topology."

In my view, we are faced in biology with the same crucial difficulties as in theoretical programming:

1) With respect to the problem of origins, the impossibility of sifting (within less than 10^{100} cycles, say, for non-trivial cases) from mere typographic variants the ones which are syntactically correct, except by using algorithms in which the very concept of syntactic correctness has been incorporated.

2) Granted such a syntactic device, the present lack of a conceivable mechanism which would insure within an interesting range the faintest amount of matching between the two above mentioned topologies (this is said notwithstanding claims to the contrary of some "artificial intelligence" teams).

In other words, I believe that an entirely new set of rules is needed to obtain the sort of correspondence which is assumed to hold (one way—Darwin, or the other—Lamarck) between neighboring phenotypes and which is needed in similar theories of evolutions. If these new principles, or deductions from old ones, were to be postulated, it would seem then a subsidiary point to discuss how much of random mutations and selections are at work in conjunction with them.

Indications of Order in α Model of Prebiotic Protein-like Polymer

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All of the amino acids common to protein can be condensed in the laboratory under conditions which are simple and otherwise imputable to spontaneous reactions on the primitive Earth. The polymers have molecular weights of many thousands, contain some proportion of each proteinogenous amino acid, and have many other properties of contemporary protein. In particular, they easily organize, on contact with water, into models of the protocell, with many of the properties of the contemporary cell (1).

This last behavior suggests that thermal polyanhydro-α-amino acids represent stuff appropriate to the spontaneous generation of the first cell. These demonstrations are a particularization of a more general explanation stated by Wald in 1954.

Examination of such polymers—by reprecipitation from water, by fractionation on DEAE-cellulose, by gel electrophoresis, by high voltage electrophoresis, on BioGel columns, on Sephadex columns, by ultracentrifugation, and by amino acid analysis of fractions—reveal that the polymers are of sharply limited heterogeneity. Comparisons of N-terminal, C-terminal, and total amino acid compositions indicate a nonrandom distribution of amino acid residues in the peptide chains of the unfractionated polymers.

Properties of cells arising from primordial polyanhydro-α-amino acids would be, according to the model, derived directly from the properties of the polymers. Results of experiments at the molecular, macromolecular, and morphological levels are interpreted to signify that the processes of prebiotic evolution were sharply self-limiting. Such processes can be referred to the limited heterogeneity, composition, and structures of the first polymers.

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On Some Practical Consequences of the Existence of Evolution Laws in Physical Chemistry of Energetically Open Systems

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The opposition between laws which govern the behavior and evolution of so-called living systems and those which define transformations of physico-chemical systems has been put forth frequently. Results of such discussions have generally been used in order to adopt more or less irrational positions about the problem of the origins of living beings.

The aim of this paper is to show that such a frame of mind corresponds to the adoption of a dogmatic position in regard to macroscopic laws of energetics. According to this position, the only laws which are taken into account are those which define the state of isolated systems. On the contrary, quite in opposition to this point of view, the consideration of some recent acquisitions concerning the behavior of energetically open systems brings out some remarkable correspondences between the fields of the "living" and the "non-living."

From an axiomatic point of view, only a part of the new laws necessary to treat the subject as a whole has been recently proposed in connection with thermodynamics of irreversible phenomena. From a biophysical standpoint, the most important of these laws is probably the entropic criterion of evolution of open systems which was proposed last year by Glansdorff and Prigogine (1, 2).

According to this evolution criterion, a part of internal entropy production related to fluxes in the systems cannot but decrease with time as their evolution is progressing. It seems reasonable to transpose this acquisition by saying that in open systems, compounds or internal structures different from equilibrium ones spontaneously arise, which may be considered to have no "raison d' être" other than bending this entropy production in the way of minimalization.

Unfortunately, in the present state of knowledge, nearly no quantitative discussions have been sufficiently developed and analyzed about correspondences of this theorem to the selection of states acquired by the systems to perform this evolution (2). Nevertheless, it is now possible to use the general concept underlying such a point of view for developing a coordinated survey of some recent hypotheses concerning the origin of living systems.

This development will be based upon the following statements (3):

—It is possible to develop a general discussion which brings together all steps of evolution of the earth surface from a primordial state to a non-precise level, located somewhere later than the formation of elementary living beings. Indeed there may be no upper limit against time to the validity of such a discussion. Therefore this theory tends to integrate processes corresponding to chemical evolution and to evolution of properly termed living systems.

—In such a development, the formation of living systems is taken into account as the result of a necessity.

—The vocabulary of the qualitative and quantitative developments of such a theory is principally the one corresponding to macroscopic physics of energetically open systems.

—Considering the earth periphery as a whole, this evolution has been and is governed by a prime cause, associated with the nature of the average conditions im-

posed on this system. It was not and is not dependent upon macroscopically aleatory fluctuations of local state, with respect to time or geography.

—Considering the earth periphery as a whole, this prime cause has been and remains the continuous feeding of energy, mainly of solar origin, imposed on this system.

—A secondary cause of evolution of the biosphere has been selection against mass of hydrogen in respect to gas diffusion from the atmosphere to outer space.

—Considering any subsystems, taken separately within the biosphere, and able to present any type of evolutive characters, the cause of this evolution must be defined as some continuous feeding of energy imposed on the subsystems from their environment.

In applying these concepts to the discussion of the continuous formation of more and more complex systems arising from an initial state, corresponding to the primordial atmosphere, we will have to retain some recently proposed suggestions as to the development of chemical evolution; whereas some other ones will become inadequate and will have to be replaced.

First of all, it is certain that there are no objections to be raised against proposals concerning the formation in primordial conditions of biologically valuable micromolecules under the influence of different types of hard energy fluxes. A sufficiently large number of experiments are known in this field. It is possible from these to specify that any continuous feeding of energy, containing spectral fractions harder than 10 to 12 V. E. in a hydrogenated mixture of gases and partially condensed water, gives rise to the formation of practically all of the most important types of biomolecules. Alpha-amino acids and pyrimidic and puric bases are the most representative among these compounds. This step of "micromolecular evolution" may be analyzed, and it is possible to show that it corresponds to the succession of two types of processes.

During the first, located primarily in the outer layers of the atmosphere, were formed unsaturated molecules containing probably no more than 2 or 3 atoms of carbon, nitrogen and ozygen. It is possible to reproduce *in vitro* very easily such conversions of methane, ammonia and water vapor by keeping such mixtures some seconds under the action of silent discharge at pressures of some centimeters of mercury. Very high conversion outputs, higher than 50%, may thus be obtained.

During a second part of the micromolecular evolution these unsaturated gases were dissolved and so become able to polymerize. According to our point of view, the result of this process must certainly be very different, whether it operates by simple chemical relaxation, or under a flux of assimilable light. In the primordial conditions, α-amino acids and nucleic bases were formed among many other biochemicals. In the present state of knowledge it is impossible to tell if, as early as that time, systems were sufficiently complex to let selection rules favor some reaction processes over others.

From the state so obtained, many different proposals were advanced to discuss the formation of prebiological macromolecules such as polypeptides. All these hypotheses have in common that they imply primordial mechanisms for condensing micromolecules, for example α-amino acids, which have absolutely no common points, even qualitatively, with the actual ones. According to our general statement, we have to admit that, starting from the state previously obtained, a subsequent evolution of the primordial system under ultraviolet and visible energy feeding, has taken place.

From our preliminary studies, the analysis of this process first implies the conversion into an excited state of amino acids in buffered aqueous solutions, either directly by absorption of photons near 2200 Å, or by an energy transfer from polyphosphoric systems synthesized themselves from photochemical conversion. The energy-rich state of the molecule thus obtained may then be relaxed by otherwise endergonic condensation with another molecule. This process is greatly favored if the two condensing molecules are weakly fixed from the beginning, close to each other on a complexing system, either mineral or organic.

It is thus possible to propose several successive mechanisms of condensation, more and more complicated, from the first one:

a) One molecule of α-amino acid anion A^- in aqueous solution directly excited according to:

$A^- + hv$ (2200 Å) $\rightarrow$ Å + electron keeps its energy content until it comes into contact and condenses with another one.

b) This process is highly favored if the two molecules are, from the beginning, located close to each other on the same complex ion (metallic cation or organic molecule). Simultaneously, energy absorption becomes possible at higher wavelengths. The "matrix" function is thus added at this level.

c) The energy may be obtained not directly from light, but from another condensed system which may be considered an energy reserve. Here we have already shown that all types of phosphate ions may be photochemically excited, probably by the same electronic transfer process as with many other simple anions, which would lead to condensation.

d) If, in the solutions, polyconjugated molecules are present, they may and do absorb light at higher wavelength than simple anions; but are afterwards likely to lose this energy by a transfer onto molecules which can condense. This corresponds to a "photosensibilisator" function.

From the first mechanism to the last, new essential types of biological functions, all integrated in the only mechanism corresponding to the first process, are gradually separated one from the other. This separation became possible as new products appear, a result of the progress of micromolecular evolution, and these are able to perform a new type of reaction set which is more favorable when compared with general physico-chemical evolution criteria.

To this initial frame, new types of intermediates were added, as more and more elaborate products and structures became available. These latter have first been obtained through relatively simple ways, but their concentrations have increased in direct connection with their usefulness in metabolic pathways.

The aggregate result of these foregoing evolution steps consists of the formation of small organic molecules and of macromolecular species corresponding to an increased molecular weight. In such systems coacervation is a single general equilibrium property, and it was previously proposed to take it into consideration as the start of further evolution processes.

The fundamental problem is then to discuss the rules governing the conversion of any type of coacervate droplets into organized systems with rough cellular functions. It is possible also to focus such discussion on the fact that the coacervates have since their formation been in conditions such that they may be individually considered as energetically open systems.

Owing to the chemical evolution, before and after the appearance of coacervates, energy was continuously stored in the primordial biosphere. Macro- and micromolecular species which formed the metastable components of coacervates are themselves built up with a part of this energy. However another important part was continuously created by the solar flux into the surrounding medium, and among the compounds corresponding to this part some were less stable after their dissolution to the coacervated phase than in aqueous surroundings. Elementary metabolisms were thus possible on this basis at the scale of the coacervates. These metabolisms involve the following succession of steps:

1) —Dissolution of relatively unstable species from aqueous medium in a coacervate.

2) —Relaxation of their chemical energy within the coacervate.

3) —Exhaustion of products in aqueous surroundings.

From this basis, the origin of cellular structure must be discussed in relation to the existence of such a primordial metabolism.

First of all, some experiments in electrochemistry, made with systems and under conditions reasonably comparable to the ones involved in this step of evolution have shown that some modifications of the internal structure and of peripheral layers of the coacervates have to emerge in such conditions. These modifications correspond to the acquisition of structural features "apparently designed" to operate in the way of an optimization on the energetic characters of primordial metabolism, especially those corresponding to mass transport in the coacervate.

There is another very important point, whose discussion in the present state lacks available fundamental data. This point concerns the transition between the primordial, or completely heterotrophic way, in which biochemicals (micro- or macromolecular) were synthesized and the autotrophic way in which many more of these were obtained later. A typical case of such an evolution of reaction site is the polypeptidic synthesis.

Nevertheless, the quantitative analysis of this step is not beyond the scope of discussion in the general frame corresponding to our theory. Two methods may be used on this occasion.

The first consists in treating it as a problem of substitution of a primordial reaction process by another one, in which compounds entering into reaction do it by the way of association with a complexing system. Here this system is the coacervate itself, considered as a whole.

The second one involves a comparison between kinetic characters of biosynthesis, according as these processes are developed in aqueous solutions or in more complicated solvents, corresponding to the internal composition of coacervates.

In the present state of knowledge, too many important elements concerning the quantitative kinetics of primordial synthesis are missing to enter upon an analysis of this shift from hetero- to autotrophic biosynthesis; but no unsurmountable difficulties appear to prevent our treating it as a purely physico-chemical one. This fact is fundamental to an attack on the problem of physico-chemical significance of the acquisition and conservation of the genetic information, for such a concept has a meaning only when the systems studied can by themselves synthesize the products they need.

To end with a discussion of the properties that it is possible to bring out of the analysis of the evolution of energetically open systems, it is possible to justify the appearance of animation characters among the properties of some of the protocellular systems previously introduced by taking account of experimental facts.

From a physico-chemical point of view, animation of a system may be defined as the appearance of rhythmic response when the system is maintained openly, under continuous non-varying stresses from its surrounding. It corresponds, in the case of electrochemical systems, to oscillating behavior when maintained under continuous electrical or chemical stresses. Lately, experimental and analytical data have been available to account for such properties in the case of systems made of materials closely comparable to those involved in both the primordial and present biosynthesis.

In conclusion, we have tried to show that it is highly valuable to integrate the discussion of the origin of any of the characters of so-called living systems in the frame offered by new ideas on the energetics of open systems. At the present time, quantitative theorems and data are lacking to make precise many of the points of view involved in such an analysis. The aim of the research activity we undertook in our laboratory is to build from axiomatic origins, as well as from experimental analysis of major steps of biogenesis, quantitative developments designed to show that as many as possible of the so-called anomalous characters of living systems can perfectly well be justified from new positions in macroscopic physics.

The mathematical challenge we must overcome in this field corresponds to new necessities arising from the analysis of evolutive properties of systems in which, by nature, many coupled processes have to be taken into consideration simultaneously. At the present level of development of this research, the problems that do arise are almost restricted to the axiomatic quest of general properties of such systems alone. The experimental aspects are mainly concerned with the setting in quantitative evidence of some of the most fundamental simple processes involved in our discussion of the problem of origin and significance of life.

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L'Evolution Considérée par un Botaniste-Cytologiste

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En écrivant ces brèves pages de résumé, j'ai cédé aux amicales sollicitations de mon Collègue, Mr. le Pr. M. P. Schutzenberger ainsi qu'à la courtoise invitation du Dr. Martin M. Kaplan. C'est à eux qu'incombera la faute d'avoir introduit un béotien dans une réunion aussi savante que ce Symposium d'orientation mathématique sur l'interprétation de l'évolution des êtres vivants. En effet, je ne suis aucunement mathématicien et c'est seulement un spécialiste de la biologie végétale et de la cytologie qui se propose de vous présenter quelques vues pas toujours très orthodoxes (dans la mesure où elles sont non néo-darwiniennes) sur les facteurs qui ont pu régir la diversification des espèces. Je me permettrai également de faire quelques remarques relatives à la génèse de l'organisation biologique et je m'inquiéterai de façon générale de la difficulté qu'éprouve tout étudiant de la Nature à éviter l'emploi conscient ou non des concepts plus ou moins téléologiques d'utilité, de convenance, de "fitness," d'adaptation, de perfectionnement, de progrès, de "rationalisation des systèmes" que l'on rencontre dans la plupart des exposés sur l'évolution et sur l'origine des êtres vivants.

Tout d'abord, l'explication de l'évolution des végétaux et plus spécialement des Angiospermes, ou plantes à fleurs, pour nous limiter à un groupe de dimensions relativement restreints et assez homogènes, est-elle justiciable de la théorie néo-darwinienne? Il existe divers catéchismes répondant par l'affirmative à la question posée, dont l'excellent ouvrage de Stebbins (12). Les arguments sont trop connus pour que je les reprenne ici, même en les résumant.

A ma connaissance un seul homme dans le passé a osé attaquer systématiquement et avec vigueur la doctrine Darwinienne de l'évolution fondée sur les petites variations d'espèces sommées par la sélection naturelle. Il s'agit de J. C. Willis (15) dont les ouvrages méritent d'être relus, ou plutôt lus, car cet auteur est trop rarement cité et méconnu. Son oeuvre est essentiellement fondée sur une étude quantitative de la répartition géographique des familles, genres et espèces qui n'est pas favorable à la théorie Darwinienne. L'essentiel de la théorie de Willis se résume en peu de phrases. L'évolution ne s'est pas opérée à partir de la sous-espèce vers le genre mais, au contraire, à partir d'unités systématiques de rang supérieur à l'espèce. L'évolution est une conséquence de l'apparition de la vie elle-même; elle est une sorte de "développement" de propriétés (elle reprend son sens étymologique, "*evolvere*") qui présente parfois un caractère quasi inéluctable; elle possède des lois propres et en grande partie internes à l'être vivant. Willis a qualifié de *Kaleidoscopique,* ce type d'évolution où les caractères s'assortissent comme le font des débris de verre ou de papier colorés dans un kaleiodoscope. Ceci s'applique à ce petit groupe qu'est celui des Angiospermes. Willis a été très impressionné au début de sa carrière par l'étude de la famille des Podostémonacées qui présente un très grand nombre d'espèces variées bien que vivant toutes dans un milieu de chutes d'eau et de cascades, exactement dans les mêmes conditions, ce qui exclut totalement le sélection naturelle. D'après Willis l'individu possède un très grand nombre de possibilités ou de caractères á l'état latent. La tératologie peut réaliser une foule de combinaisons inconnues dans la nature faisant passer les formes d'un groupe à l'autre, franchissant facilement non seulement les barrières de

l'espèce mais encore celles du genre et de la famille. Parfois même, dans la nature, certaines réalisations morphologiques "détonnent" par leur présence dans une famille; ce n'est pas la sélection naturelle qui a travaillé mais la recombinaison aléatoire des caractères.

J'ai apporté une contribution personnelle à l'étude de cette question en démontrant expérimentalement que beaucoup de particularités structurales importantes de la constitution des plantes à fleurs peuvent en effet s'assortir de façon combinatoire et indépendante de la sélection naturelle à partir de caractères latents que l'on peut forcer *ad libitum* à s'exprimer grâce à l'action de substances morphogènes du type de l'acide 2,4-dichlorophénoxyacétique. On s'aperçoit que la plupart des familles de monocotylédones et de dicotylédones ont les mêmes potentialités morphologiques générales. Citons l'acquisition de la soudure des étamines (monadelphie), l'acquisition de la "couronne" (comme chez les Narcisses) ou de dispositifs évoquant les nectaires, la soudure des pétales chez les plantes où ces pièces sont libres. Cette résurgence de caractères latents peut être provoquée non seulement dans le domaine floral mais aussi dans le domaine foliaire. Ainsi, sur le plan phénotypique nous approchons les espèces, les genres et mêmes les familles, quel que soit leur degré d'éloignement et, de plus, nous n'observons pas de différences entre les caractères exprimés phénotypiquement par l'expérience et ceux fixés génotypiquement par la nature. Parmi ces derniers beaucoup ne sont pas nécéssaires ni même utiles; leur valeur biologique est indifférente, aussi la diversification des formes n'est elle pas toujours en relation avec un principe de perfectionnement.

Pourquoi, côte à côte, le Persil (Parsley) et la Laitue (Lettuce)? Qu'on n'insinue pas que c'est seulement parce que le jardinier a semé côte à côte ces plantes dans le jardin! Dans la nature, en effet, on rencontrera dans le même type d'habitat des Ombellifères à feuilles très divisées à côté d'un représentant étrange de cette famille, l'*Hydrocotyle umbellatum* dont les feuilles sont entières et peltées (une feuille peltée possède un limbe circulaire et un pétiole inséré perpendiculairement sous ce dernier). Et d'ailleurs, pourquoi des feuilles peltées, comme celles de la Capucine et de l'Hydrocotyle? L'auteur de ces lignes a montré que la répartition de ce caractère morphologique chez les Angiospermes était sporadique, entièrement aléatoire et sans relation avec la sélection naturelle. De plus, la peltation doit être considérée comme le fruit d'une sorte d'erreur permanente des gènes au stade végétatif: il s'agit de la réalisation hétérochronique d'un caractère morphologique qui, dans un assez grand nombre de cas, est associé à la sexualisation femelle (carpelles peltés). La peltation au stade végétatif n'est d'aucune utilité et la sélection n'a pu avoir aucune prise sur elle, ni pour l'éliminer, ni pour la conserver; seuls des facteurs internes rendent compte de son existence selon des lois qui restent à déterminer. Si la sélection naturelle ne joue aucun rôle et si l'explication que nous donnons n'est pas bonne, l'existence des feuilles peltées devra alors être considérée comme un *jeu de la nature,* ce qui est un peu gênant en ce dernier tiers du vingtième siècle.

Je n'insiste pas sur d'autres exemples qui pourraient enrichir ces vues à l'encontre de l'explication darwinienne car ils sont trop nombreux. La fécondation s'opère-t-elle plus mal chez les pavots à étamines libres que chez les roses trémières à étamines soudées? Et quel, est l'intérêt de la corolle gamopétale dans une certaine variété de pavot?

Considérons maintenant des problèmes encore plus complexes tels que ceux posés par les plantes carnivores et par la fécondation des plantes supérieures par les insectes ou les oiseaux. Des Niagaras d'encre ont coulé à propos de ces sujets. *A priori* la carnivorie aurait pu intéresser beaucoup de plantes mais elle est très rare bien que les néo-darwiniens insistent beaucoup sur la fréquence et l'intimité des relations entre insectes et plantes. Pourquoi si peu de plantes carnivores? On nous répondra certes que les plantes, en vue de la fécondation, avaient plus d'avantage à laisser les insectes en vie qu'à les utiliser comme aliment; mais les insectes (ou leurs larves) ne

commettent-ils pas bien des méfaits? N'est-ce point précisément pour échapper à certains de ces méfaits que les plantes, selon les néo-darwiniens ont inventé les carpelles? D'après Takhtajan (13), les insectes, très mal élevés, dévoraient les ovules des plantes à fleurs bien qu'ils contribuassent déjà sans doute à féconder ceux qu'ils ne mangeaient pas; courroucées les plantes à fleur refermèrent leurs carpelles et inventèrent ainsi l'angiospermie comme vous ou moi l'auriez fait. N'est-ce point exagéré, même pour un néo-darwinien, que de raconter ainsi l'histoire naturelle? Ce n'est pas Bernardin de Saint-Pierre (1), dont quelqu'un a dit que chez lui la niaiserie, s'est élevée jusqu'au génie, qui est l'auteur de ce roman ingénieux, mais le néo-darwinisme.

Pour en revenir aux plantes carnivores du type des *Sarracenia* et des *Nepenthes,* j'ai souligné que leurs urnes en forme de pièges ne sont pas des nouveautés adaptatives mais sont probablement le simple résultat de l'expression anachronique d'un caractère sexuel comme dans le cas des feuilles peltées. Formations presque closes, les urnes peuvent être considérées comme des sortes de carpelles géants, néoténiques et stériles tant bien que mal utilisés à d'autres fins par la plante (Gavaudan, 6), (Dupuy, 3). N'oublions pas non plus notre problème de l'entomophilie chez les plantes à fleurs. A en croire les néo-darwiniens ce sont les insectes qui ont modelé les plantes à fleurs. Certes existe-t-il un mystère relatif aux convenances mutuelles entre insectes et plantes mais il ne faut pas le résoudre par une théorie d'expression caricaturale; il ne faut pas nous dire crûment que les pétales ont été créés pour attirer les insectes, il ne faut pas nous dire littéralement, comme l'a fait Julian Huxley (8) que les abeilles, incapables de fabriquer des corbeilles pour rapporter le pollen, ont formé des organes leur tenant lieu d'ustensiles (Loc. cit, p. 20-21). Nous retombons de fait dans les Harmonies de la Nature de Bernardin de Saint-Pierre et nous n'avons plus le droit de nous moquer de lui ni de son langage romantique.

Nous devons maintenant faire partiellement le point. D'une part, nous constatons qu'une foule de particularités morphologiques semblent réellement sans rapport avec la sélection naturelle, d'autre part, nous voyons qu'il existe des problèmes extrèmement complexes comme ceux des plantes carnivores, de l'entomophilie des racines aériennes et de la vivaparie des plantes de la Mangrove, des plantes grimpantes à vrilles qui sont présentés parfois caricaturalement dans la doctrine néo-darwinienne qui est incapable de donner plus qu'une description romancée de l'origine de ces dispositions remarquables.

Il existe une foule de mystères biologiques que nous ne comprenons pas encore. La lumière produite par les photobactéries est-elle utile à celles-ci? On a parlé d'un mécanisme, aujourd'hui vestigial mais autrefois utile, pour éliminer l'oxygène qui était un gaz toxique à l'aurore de la vie (McElroy et Seliger (4)). Ou bien, penserons-nous que les bactéries ont horreur de l'obscurité? Par contre, sans doute, certains poissons sont-ils lumineux dans les profondeurs pour voir et être vus. Poissons, Cephalopodes et Crustacés possèdent des photophores qui sont de véritables projecteurs avec couche d'émission, miroir et lentille? Tout celà est bien étrange et apparait plus comme le fruit d'une loi générale de réaction à l'obscurité que comme celui de la sélection naturelle. La Sensitive a des possibilités de mouvements très rapides qui ne lui servent à rien mais des mouvements analogues sont utilisés par la Dionée pour piéger des insectes. Ainsi la nature exploite-t'elle ou laisse-t'elle de côté les mêmes possibilités avec plus ou moins de suite dans des idées.

Mais la grande "idée" de la nature n'a-t'elle pas été la vie elle-même dont nous essayons de percer le secret et l'origine. Comment la vie est-elle apparue? Oparin (10), suivi dans cette voie par Calvin (2) Pullman (11) et d'autres encore, a mis en avant la doctrine de la sélection naturelle qui est décidément bonne à tout faire. D'application déjà incertaine dans l'étude de l'évolution nous la voyons mise à contribution pour expliquer les origines de la vie.

On nous explique, par exemple, qu'une sélection des coacervats les plus stables, puis de ceux dont l'organisation dynamique était la meilleure, a eu lieu, ou que les molécules à électrons délocalisés ont été les plus aptes à constituer les premiers systèmes vivants.

Dans des commentaires que j'ai ajoutés à la traduction francaise de l'ouvrage d'Oparin (10) je me suis enquis de la validité de l'emploi de la notion de sélection naturelle en tant que principe essentiel pouvant conduire à expliquer l'origine de la vie. Peter Mora (9) s'est élevé avec fougue contre ce qu'il a appelé "the folly of probability." Citons également les divers points de vue de Elsasser (5) et de Wigner (14). Nous voyons les physiciens se montrer beaucoup plus circonspects et plus nuancés que les biologistes qui nous donnent des explications simples et immédiatement mécanicistes de la vie et de son origine.

Il est évident que dans beaucoup de cas, que nous soyons néo-darwiniens ou non, l'existence de certaines adaptations nous émerveille. La pensée téléologique habite à peu près sans exception tous les scientifiques, à leur insu ou non, à peine un peu moins que chez Bernardin de Saint-Pierre, ceci quelle que soit leur philosophie générale. Le langage tout au moins est le même et ceci est grave. Un des problèmes fondamentaux à résoudre est celui de l'aspect téléologique des systèmes vivants. Ainsi le terme "purposefulness" revient-il sans cesse dans l'ouvrage d'Oparin sur l'origine de la vie sur la Terre, bien que son Auteur nous ait averti qu'il ne veut pas l'utiliser dans un sens idéaliste. Il nous dit cependant que le métabolisme est "rationnel," que "les organes du protoplasme vivant sont construits d'une façon parfaitement rationnelle (Loc. cit. p. 227)" "que le métabolisme est comme un réseau routier construit rationnellement (Loc. cit. p. 315)," que "la sélection naturelle a renforcé la rationalisation des systèmes (Loc. cit. p. 324)." Un physicien dit-il que la chute des corps est rationnelle? En fait, elle est indifférente, elle obéit à une loi à laquelle nous n'appliquons pas de jugement de valeur. Mais le caractère extraordinaire du système vivant, si plein de "fitness," provoque l'étonnement de tout chercheur.

Sans aucunement refuser toute place à la sélection naturelle en tant que crible, pourquoi n'existerait-il pas un plan général dans la nature qui rende compte à la fois du "fitness of environment" de Henderson (7) et du "fitness" des systèmes vivants tel qu'il préoccupe Oparin?

Les systèmes vivants sont des ilôts de complexité maxima dans l'Univers réunissant toutes les complexifications plus une, la vie. Dans ces conditions il n'y a rien d'étonnant à ce que nos idées ne puissent encore être bien claires et à ce que la vie ne puisse être déductible rationnellement à partir d'un petit nombre de données fondamentales simples que nous ne connaissons d'ailleurs qu'imparfaitement. La prétention du néo-darwinisme à nous ouvrir à lui seul la porte de la vérité apparait un peu puérile. Peut-être l'évolution du monde vivant était-elle aussi inéluctable que celle du monde atomique? Peut-être la série qui conduisit de l'Hipparion au Cheval était-elle aussi marquée par la nécessité que l'est la série de désintégration des éléments radioactifs?

Je terminerai en donnant simplement l'idée que j'ai de la complexité du problème de l'évolution en songeant encore à l'origine de la cellule. Pour connaître l'origine de cette unité ou atome de vie il faudrait en comprendre parfaitement la signification actuelle. Or, que savons-nous à ce sujet?

Je vais donner ici une recette de cuisine. Prenez un des traités de cytologie contemporains les plus exhaustifs (Brachet-Mirsky), (soit 3.500 p.), ajoutez-y les quelques 8.000 pages de l'International review of Cytology et les quelques 30.000 pages du Journal of Biophysical and Biochemical Cytology dont le titre s'est mué en Journal of Cell Biology; condimentez avec d'autres milliers de pages du beau traité de Sumner et Myrback sur les Enzymes et quelques traités de Biochimie du meilleur cru (Florkin et Stoz, Florkin et Mason).

Vous avez alors à votre disposition pour autant qu'un décompte sommaire du nombre de pages et un calcul rapide soient exacts, environ 200 kilomètres de phrases contenant des énumérations et inventaires, des tableaux de nombres ou de chiffres, des diagrammes, des figures, des photographies, des propositions et relations logiques mais à peu près pas de lois ou de théorèmes vraiment généraux propres à la vie elle-même. Que peut-on tirer de ce ragout ou de ce cocktail? Tout ce kilomètrage d'informations laisse de côté bien entendu une somme immense d'autres connaissances. Je veux parler des riches documentations de Biologie générale sur des centaines de mille d'espèces de plantes et d'animaux qui augmenteraient probablement de milliers de kilomètres le chemin à parcourir pour étudier ainsi la vie. Tout cet ensemble, mise à part l'indéniable réussite qu'il représente sur le plan de l'empirisme et de ses applications, ne possède cependant sur le plan de la connaissance qu'une valeur à peu près égale à celle de la Comédie Humaine de Balzac, d'un livre de cuisine ou d'un livre d'inventaire. Cet ensemble n'est encore qu'un recueil d'anecdotes ou de conseils pratiques. De plus, même en s'appliquant à lire le plus rapidement possible, tout en s'efforçant naturellement de comprendre, on marcherait le long de cette route pendant de nombreux mois. Après avoir atteint seulement la dixième ou douzième borne kilomètrique l'esprit le mieux organisé se déclarerait forfait et ayant oublié ce qu'il aurait lu et assimilé quelques kilomètres auparavant, se trouverait incapable d'établir toutes les relations utiles pour épuiser la matière de l'information et la restituer sous la forme de toutes les propositions raisonnables possibles et utiles. De plus, il n'est pas certain que les centaines ou milliers de kilomètres contiendraient tout ce qui est indispensable pour expliquer et comprendre la constitution et le fonctionnement des cellules. Nous demandons aux mathématiciens ce qu'ils pourraient faire de leur côté avec leurs machines, après entente avec les biologistes pour la programmation. Songeons qu'auprès de ce ruban de plusieurs centaines de kilomètres d'information la cellule se mesure seulement en microns, centaines de microns de longueur (quelquefois en centimètres pour certaines exceptions remarquables). La disproportion est énorme entre l'espace que nous devons utiliser pour rendre compte de l'organisation d'une petite cellule et les dimensions même de ce dernier objet.

Par ailleurs, des milliards de neurones contenus dans les cerveaux humains essayent de se donner une image consciente de leur propre organisation. De toute façon le rendement de cette opération est actuellement très mauvais. Bien que la seule à notre disposition pour comprendre la cellule et la vie, la méthode que nous utilisons est évidemment médiocre et fastidieuse.

Cependant la cellule est une réalité qui s'est édifiée toute seule sans avoir eu besoin de toutes ces connaissances conscientes constituées par la collectivité des neurones. D'aucuns, comme nous l'avons vu, considèrent que la cellule est "rationnellement construite." Existe-t'il deux systèmes rationnels, l'un inconscient, ayant fabriqué la cellule au cours des âges révolus dans le giron de Dame Nature et un autre qui est le raison humaine recherchant le même chemin? Ou bien n'existerait-t'il qu'un seul domaine rationnel et notre raison elle-même n'est-elle autre que celle de l'Univers?

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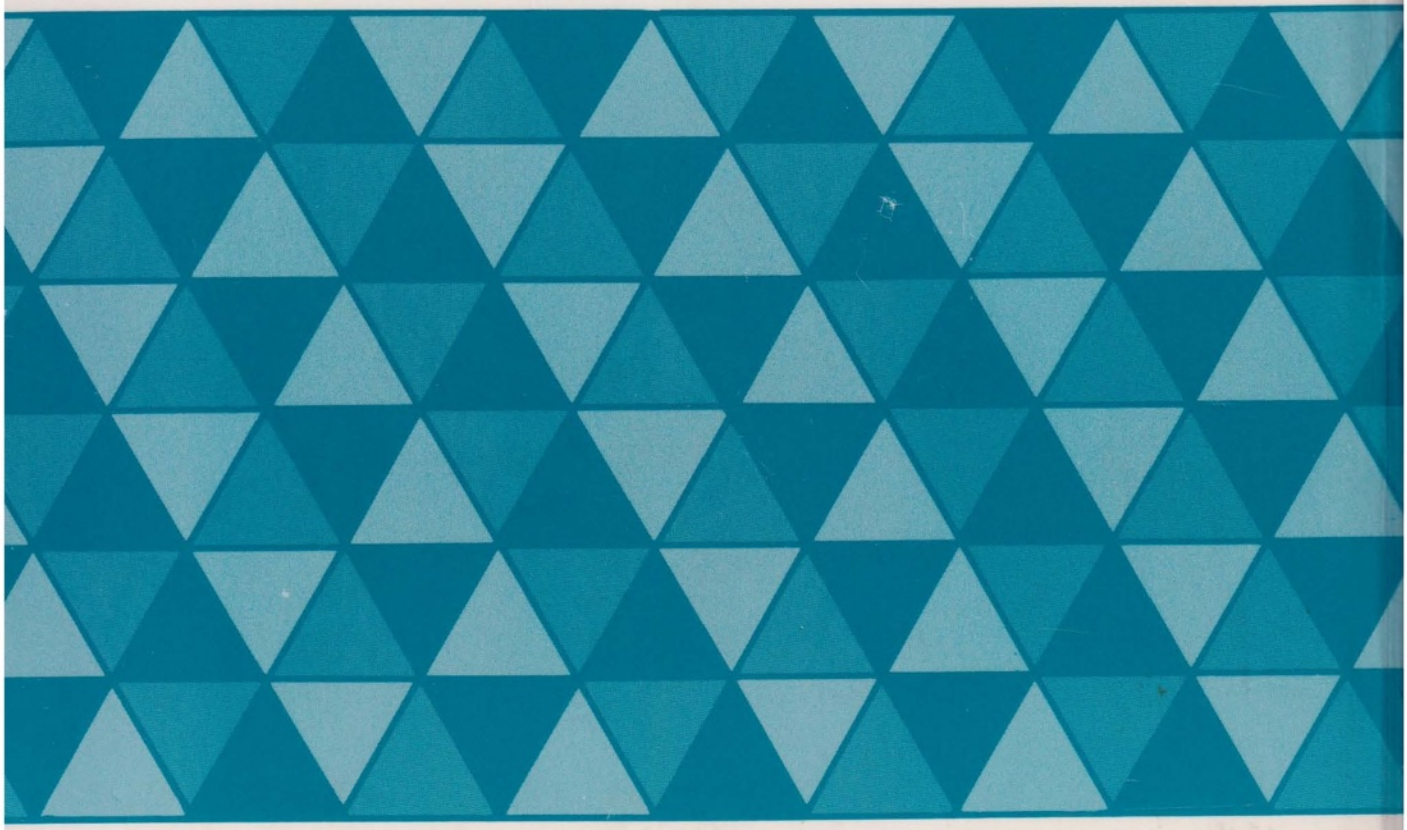

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