

INTERNAL FACTORS IN EVOLUTION

by

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(Received 15. III. 1963)

I. PRELIMINARY

This paper continues the discussion (WHYTE, 1960) of developmental selection (D.S.)¹⁾ in relation to evolution. "If genetic systems, or developmental processes or, more broadly, the conditions of biological organization in the species ever determine the actual, or restrict the possible, directions of evolutionary change, then the now prevailing form of the theory of evolution by adaptive selection and its mathematical expressions are likely to require modification — this is, generalization to include the very different effects of developmental selection". Here "evolution" means the emergence from some initial state of new forms of organic specificity forming part of a phylogenetic sequence.

D.S. was defined as an internal selection of mutations, "in which the criterion is compatibility with the internal structure and processes of the system". This internal selective process may operate at any level: molecular, chromosomal, or cellular. It probably occurs mainly during the earliest phases of growth and the first cell divisions and hence, in species with

1) The following abbreviations are used:

D.S. (developmental selection). The internal selection of mutated genotypes and their consequences, the criterion being compatibility with the coordination of the internal structure and processes of the organism. The restriction of the otherwise possible directions of evolutionary change by organizational factors within the organism.

A.S. (adaptive selection). The external Darwinian selection of mutated phenotypes, the criterion being competitive reproductive efficiency in a given environment. The restriction of the directions of change permitted by D.S., by factors involving the relation of the organism to external conditions.

C.C. (coordinative conditions). The general mathematical conditions satisfied by all viable biological organization; the rules of spatio-temporal ordering which must be met by the internal parts and processes of any organism viable in an appropriate environment. The C.C. define a universal form of ordering; different organisms represent different specific realizations of that universal form; evolution is the passage from one specific realization to another.

a protected phase, prior to external adaptive selection (A.S.). But it is not possible to separate (i) determination by the genome of the directions or rates of mutation, and (ii) the internal developmental selection of undirected mutations. In both processes the general conditions of organization necessary to all organisms and the specific genetic system of the individual impose restrictions on the modified genomes which can develop from pre-mutational disturbances of the genome into new reproductive phenotypes.

D.S. is a new type of natural selection, *i.e.*, an extension to the internal environment of the Darwinian selection of phenotypes in the external environment. This extension is so natural that at first sight it might be considered not to involve a new principle. We shall see that this is not so, because D.S. involves structural factors alien to the theory of the A.S.

Four influences may affect phylogeny: (i) genomic partial determination of mutations and/or their rates; (ii) genomic selection of mutations through the first few divisions, *i.e.*, before the early phenotype begins to manifest itself; (iii) developmental selection (in a narrow sense) of an emerging protected phenotype; and (iv) external adaptive selection of an unprotected phenotype. (i), (ii), and (iii) are separable only with difficulty and may for the present conveniently be grouped together as *d e v e l o p m e n t a l s e l e c t i o n*, since they all represent the influence of internal factors closely related to ontogenetic development.

We shall therefore concern ourselves with internal selection, *i.e.*, with D.S. in a comprehensive sense: the restriction of the possible directions of evolutionary change by factors internal to the organism. In contrast to the external adaptive factors these internal factors are structural and organizational and may operate either by focussing premutational disturbances so as to produce directed mutations, or by selecting from undirected mutations those which result in adequately coordinated mutated genotypes capable of successful development. (Here the term mutation covers any inherited change in specificity due to disturbances, recombination, *etc.*). The most significant phases of this internal partial determination and/or selection occur during the early history of the germ cell or of the zygote. However the basic distinction between D.S. and A.S. does not depend on the period in which they occur, but on the contrasted character of the criteria determining the two selective processes. There is a genome "homeostasis" in the individual, which does not resist all changes but stabilizes those genomes satisfying certain conditions, and is distinct from the genetic homeostasis of populations. For example, the criterion which determines whether or not a mutated genome is capable of coordinated self-replication and of any other catalytic actions bears no relation to the criterion that an adequate eco-

logical niche must exist for the corresponding mutated phenotype.

One purpose of this paper is to examine the validity and scope of this distinction between D.S. and A.S. in relation to evolutionary change. While the elimination of deleterious mutations during development is well known, the ability of only certain classes of mutations to replicate, to survive development, and to produce new phenotypes may prove as important for evolutionary theory, and is less understood.

The elimination of harmful mutations and the preservation of neutral or favourable mutations leading to new varieties of phenotypes (*e.g.*, more highly differentiated) are not complementary aspects of a single process. In the first a failure is eliminated; in the second a successful novelty is preserved. These are distinct processes in individuals, as different as are death and continued reproduction, and each can occur without the other. Though little is yet known of the criterion which distinguishes a successful from an unsuccessful variation, the difference in the results is crucial. For successful differentiative mutations are the source of phylogeny. While lethal mutations and hybrid inviability or sterility have long been known, relatively few successful differentiative mutations have yet been identified and investigated.

Thus in passing from the A.S. of harmful mutations — the area most fully investigated so far — to the D.S. of favourable or differentiative mutations (for which no test is yet available) a double shift of attention is involved. We have to consider first the favourable mutations which have not been identified as yet, and second their relation to D.S., a process only studied up to now in relation to harmful mutations. This double reorientation of viewpoint may be difficult, but it is necessary once it is realized that D.S. must in some degree contribute to determining the possible paths of phylogeny. Selection is the differential reproduction of genotypes, and there is no reason to assume, as in the standard theory, that this selection operates solely on phenotypes.

Three assumptions will be made:

A. That the neo-Darwinian and Mendelian synthetic theory of evolution by adaptive selection, as developed 1920/1950, covers certain necessary conditions for a history of terrestrial life, *i.e.*, those relating to the external aspects of processes involved.

B. That this theory does not cover sufficient conditions for a comprehensive theory of the history of life, since a structural theory of mutations and of ontogenetic development is lacking.

C. That it is not yet known to what extent, or in relation to what aspects, individual mutations when they occur are undirected, *i.e.*, lack a significant

correlation with the adaptive properties of the corresponding phenotype.

If internal factors restrict the possible directions of evolutionary change, this does not justify any prejudicial finalistic philosophy of organism or the limitation of the causes of evolution to any one class of factors. The operation of internal factors as here conceived is not vitalistic, since it involves potentially observable structural parameters; nor orthogenetic, since it allows many avenues of potential evolution; nor nomogenetic (BERG, 1926) since it is complementary and not alternative to the operation of external factors. Attention to internal factors is a natural consequence of the organicist view which regards the characteristics of organisms as consequences of a state of organization in complex structured systems of certain kinds in appropriate environments. On this view the genome may not only be a self-regulating and self-repairing system (*e.g.*, restitution by return of minor deleterious mutations), but in some degree determine its own viable transformations.

It is of importance that the most appropriate general term be used to designate the characteristic structural ordering or spatio-temporal coordination of parts and processes within all living systems. Here coordination is selected as preferable to organization, ordering, correlation, integration, unity, coherence, balance, which may be better reserved for other purposes. The general mathematical conditions of biological coordination, *i.e.*, the rules of ordering (assumed to be discoverable and capable of rigorous formulation) which must be satisfied, to within a threshold, by the internal parts and processes of any organism capable of developing, sustaining, displacing, and reproducing itself within an appropriate external environment, will be called the coordinative conditions (C.C.).

The C.C. may be a single set which applies at all levels, or they may form a hierarchical set. They may define an aspect of invariant order which persists through all normal transformations of the organism, or they may be essentially dynamic and represent an ordering tendency or a self-ordering process. The C.C. are the mathematical expression of the general organic conditions which in the genome lead to its homeostasis and consequently to developmental homeostasis. The C.C. are strong, *i.e.*, they impose a high degree of invariant order, but they are not maximal, *i.e.*, they leave some parameters free to vary. "If an organism were completely integrated developmentally in one sense of that vague term, any mutation would be grossly harmful or even lethal." (HALDANE, 1958). The C.C. can apparently be satisfied in countless contrasted specific manners, each sharply distinguished by a characteristic molecular pattern evidenced in a hierarchy

of structures. The coding of specificity originates, and is only effective, under the C.C.s.

The C. C. are best regarded as the conditions under which the basic laws of all complex structured systems permit the emergence and persistence of the phenomena of life, and not as being consequences of a past process of adaptive organic evolution. If the emergence and continuance of life was only possible provided the C.C. were met, then the C.C. cannot be merely a result of adaptive selection. The C.C.s are the general conditions characteristic of all forms of life; the particular manner in which these conditions are met determines the specificity of a given species and is progressively modified by successive mutations in the course of evolution.

The aims of this speculative exercise in theoretical microstructural biology are to elucidate the possible effect of internal factors; to suggest where and how D.S. can be separated from A.S.; and to argue that the time has come to take the internal factors seriously, since they may soon be susceptible to structural investigation, both empirically and theoretically.

The general issue with which we are concerned would only be confused by the consideration, which would be premature, of its possible relation to neighbouring problems such as systemic mutations, macroevolution, environmental or cytoplasmic influence on the genome, detailed aspects of development, *etc.* Nor will any attempt be made here to examine (i) the comparative aspects of D.S., *e.g.*, in micro-organisms, plants, and animals; (ii) the precise physical and chemical conditions determining permissible structural changes either in the DNA array or in other parts of the chromosomal system; or (iii) the relation of the C.C.s to transitional forms between inert macro-molecules and living cells.

2. HISTORICAL

A brief historical survey will throw light on the changing status of internal factors.

T. H. HUXLEY (1888) considered it "quite conceivable that every species tends to produce varieties of a limited number and kind and that the effect of natural selection is to favour the development of some of these, while it opposes the development of others, along their predetermined line of modification". Conjecture along these lines was then common. For example, A. WEISMANN (1896) outlined a theory of germinal selection, providing "a spring of definitively determined variations".

But at that time, indeed until around 1940, there was no direct evidence for such internal determination and the dominant view, say from 1910 to 1940, was that expressed by T. H. MORGAN (1919) who put the question

“Is the direction of mutation given in the constitution of the genes?”, and answered that this was “thinkable”, but not “probable”. For reasons then valid, the emphasis was placed on adaptive selection of undirected mutations; there were no observations suggesting that internal factors played any role in guiding phylogeny.

None the less a modified form of the principle rejected by MORGAN was meantime being silently introduced into evolutionary theory by the students of lethal and sub-lethal mutations, who took for granted that deleterious mutations and the resulting mutated genotypes might be eliminated during ontogeny, with the implicit corollary that developmentally viable mutated genotypes are restricted to classes determined by the genome itself and by the developmental processes which it induces. Even if mutations are originally undirected, the concept of developmentally deleterious mutations implies that some mutations are not deleterious, *i.e.*, the operation of an endogenous sifting process with its own criterion at work, as well as, and usually prior to, A.S.

Around 1930/40 three influences were preparing the way for reconsideration of the role of internal factors; — (i) It was recognized that A.S. operated not on single genes, but on the entire genetic system as a working unit, and system effects began to be investigated. (ii) It became increasingly obvious, with the development of structural biochemistry, that the organism constitutes a highly organized “environment” for genes and their mutations. (iii) Closer attention began to be paid to the relations of ontogenetic development to phylogeny, by WADDINGTON and others. Thus by 1940 the background was favorable to the examination of internal factors.

None the less between 1920 and 1960 relatively few biologists explicitly considered in a general context the possibility that the constitution of an organism may not only result in the elimination of deleterious mutations but also set restrictions to the directions of evolutionary change open to its descendants, in contradiction to the assumptions of the dominant synthetic theory. J. C. SMUTS (1926) asked “Are (variations) all individually selected before they have any survival value or strength?” “It is thus the organism, as a whole which in the first instance ‘selects’ the variation.” But this was a mere philosophical conjecture, and the attention of most working biologists concerned with the causes of evolution was concentrated on the external adaptive factors and members of the dominant school only began to re-examine the status of internal factors after 1940. Here are some of the most instructive examples: —

- T. DOBZHANSKY (1941). "— it would follow that the evolutionary courses of races and species differing in gene arrangement are likely to diverge owing to modification of the rates and possibly of the directions of mutations in certain genes".
- C. STERN (1943). (Observations on mutations suggested that) "new points of attack for selective forces would originate. — It can hardly be estimated how much of such concealed evolution (*i.e.*, internal selection leading to different genotypes, phenotypically alike) due to the kind of 'germinal selection' described, is taking place at any time."
- H. SPURWAY. (1949) "A group of related organisms is characterized by similar possibilities of mutation — these possibilities of mutation determine the evolutionary possibilities of the group, — it suggests a specific control of mutability in excess of anything we know so far. — A given species, family, or class mutate more readily towards certain phenotypes than others. — the mutation spectrum of a group may — determine its possibilities of evolution." SPURWAY (1960) suggested that a change in genetic make-up (e.g., translocation) may at once constitute an isolating mechanism, that "chromosomal sterility is direct consequence of the structure of the chromosomes" and of "the actual way in which the integrated genetic system is transmitted."
- L. V. BERTALANFFY. (1952) "Thus the changes undergone by organisms in the course of evolution do not appear to be completely fortuitous and accidental; rather they are restricted, first by the variations possible in the genes, secondly, by those possible in development, that is, in the action of the genic system, thirdly, by general laws of organization."
- A. LIMA-DE-FARIA. (1952, 1954, 1956, 1962) Certain evidence favours the view that "selection should take place not only at the organism level but at the chromosome level. — The genotype of an organism evolves under defined conditions". (1954). He suggested (1956) that "the constitution and organized pattern of a chromosome are the prime determinants of its evolutionary trend and that the genotype of an organism evolves chiefly under conditions defined by the constitution and organization of its chromosomal components."
- C. H. WADDINGTON. (1957). "There has been at least one suggestion that processes of selection may sometimes occur at the level of the gene itself. — these cases could perhaps be considered to provide examples of a category of selection which operates, not on the phenotypic results of the developmental activities of genes, but directly on the genotype itself. — These examples are, however, not very convincing."
- J. B. S. HALDANE. (1958), following SPURWAY, considered a "selection based on genotypes", a "directional evolution" not due to environmental changes, and the possibility that "the disturbance of a particular developmental process is more or less harmless in one species, but lethal or sub-lethal in another closely related one." Later (1959) he argued that "if certain mutations interrupt some important developmental process — the possibilities of evolution open to a species depend not so much on its genes and their mutability, as on its developmental processes."

An examination of these passages is instructive. SMUTS reached his notion from a holistic philosophy of organism, but left it vague and non-structural. DOBZHANSKY may have been the first geneticist explicitly to re-

introduce the conception of a probable control by the genome of its own directions of mutation, after MORGAN's repudiation of this idea in 1919. STERN observed what he interpreted as an internal selection, in this case leading to contrasted genotypes with similar phenotypes. SPURWAY inferred from observations of homologous variation the likelihood of a restricted "mutation spectrum." BERTALANFFY, an organicist philosopher, maintained the operation of a triple internal restriction on phylogenetic changes: by the permissible variations in genes, by the genetic system during development, and by the general laws of organization. LIMA-DE-FARIA (1952 onwards) inferred the presence of internal selection acting on the chromosomes from the study of chromosomal gradients and field effects, but surely went too far in regarding it as the "prime" determinant of evolutionary trends. WADDINGTON, drawn to the problem by concern with the relations of development and evolution, considered the possibility of one form of internal selection, but regarded the evidence as inadequate. HALDANE treated D.S. as a potentially important issue.

Both DOBZHANSKY and HALDANE reached the idea through consideration of the observed differences in mutation rates, these being, it seemed, genetically determined in certain cases. From this it is a small step to the partial genetic determination of the successful directions of genotypic change. SPURWAY's remarks are noteworthy, since as early as 1949 she gave clear expression to a hypothesis regarding the general importance of internal factors, reached from an analysis of examples of homologous variation, which she has since developed. Soon after LIMA-DE-FARIA ascribed an even greater role to internal factors.

These quotations represent, in this respect, the most advanced thought of the period. Many other discussions of the elimination of deleterious mutations during development implicitly involved the consequence that internal factors restrict the successful directions of evolutionary change and came to the threshold of this inference, but without passing over and making it explicit, or considering its possible general importance. For example, SCHMALHAUSEN (1949) based his theory of stabilizing selection on the ability of the mechanism of individual development to undergo changes independently of the adaptive properties of the phenotype, but did not infer that this implied restrictions on the successful changes leading to new evolutionary steps. LERNER (1954) considered developmental or ontogenetic homeostasis, but his concept of genetic homeostasis is a population property. Moreover the influence of internal factors was not mentioned as of possible evolutionary importance in any of the leading Darwin Centenary Surveys, published 1959/60, though it had been the subject of private discussion

during the 1950's, *e.g.*, by readers of SPURWAY, BERTALANFFY, and LIMA-DE-FARIA.

Thus while many special conceptions had been developed (developmental elimination of deleterious mutations, factors influencing mutagenesis, differential mutation rates, mutator genes, developmental homeostasis, developmental channels or barriers affecting the results of mutations, *etc.*) few attempts had been made to draw the general conclusion that one of the basic postulates of the synthetic theory was too restricted: the assumption that the variations undergoing A.S. were adaptively undirected. For example, if D.S. is effective it is not necessary to ascribe all the biologically significant properties of the genome (*e.g.*, linkage of genes with related functions) to past adaptive selection. They may be a direct consequence of the C.C.

The present situation is marked by a paradox of a kind frequent in the history of science: the operation of internal factors in several special contexts is already regarded as a commonplace, particularly in private discussions, but the fact that this contradicts an assumption of the general theory of evolution is unduly neglected in the literature, this being for many an emotionally charged issue.

The elimination of deleterious mutations during development was a commonplace during the 1930's. Yet the influence of internal factors in determining what can constitute successful mutations (and so phylogeny) is only in the 1960's becoming widely recognized as an important issue. This 30-year lag is instructive. The main reasons may have been: concentration on observations rather than theory; a continuing stress on statistical and ecological aspects with consequent relative neglect of the internal structural developmental processes; the absence of direct evidence regarding the character of successful mutations leading to new differentiations; and the difficulty — until the conception of the C.C. had been clearly formulated — of achieving a valid theoretical and observational separation of developmental from adaptive selection. These influences combined to stifle discussion of the relation of D.S. to phylogeny.

3. CRITIQUE

Organisms display a high degree of structural and functional coordination, a multiple cross-correlation of parts and processes, which lapses only in pathology, senescence, and death. If this characteristic biological form of ordering, including its expression in the genome, is such that it can be precisely identified, it follows that any modifications of the genome capable

of surviving development must satisfy restrictive conditions which await discovery. Even if mutations or pre-mutational disturbances are originally undirected, the ones which survive even the earliest cell divisions will be those forming part of a new well coordinated genome. "The struggle for survival of mutations begins at the moment mutation occurs" (WHYTE, 1960). The new genome must first, satisfy the general C.C., and second, not be so different from the unmutated genome as to prejudice a successful transition. Since the previous coordinated system has been discarded, a new and sufficiently accessible and stable coordination must replace it, if the mutated system is to develop successfully. Only certain classes of mutations will permit the mutated genome to satisfy the C.C. in such a manner as to permit a successful transition.

To employ a useful, but probably incorrect, analogy: Not only the general differential or other equations of life must still be satisfied, but the new particular solution of the equations which represents the mutated system must not involve too great a transition from the previous solution. Organic selection rules must determine the permissible transitions, and so restrict the paths of evolutionary change.

This partial analogy can help to clarify conjectures regarding D.S. provided it is remembered that the organism is an open system. How severe these genetic selection rules are, and to what extent and at what times they actually contributed to determining the multiple historical paths of evolution, remains to be discovered. But it is clear that there is no reason to ascribe the directions of evolutionary changes to one primary factor alone, competitive A.S., when a structural theory of organism implies that internal factors must also have played a part.

None the less the separation of internal from external factors raises difficulties which some have regarded as fundamental, I believe wrongly.

Objection A. Since there is universal interaction, the two selective processes are not separable. Internal and external environment, ontogeny and phylogeny, are aspects of a single total story: the history of the changing forms of life guided by one comprehensive process of selection. A distinction between the two has no fundamental validity.

Science advances by selecting phenomena which during certain periods, to a certain precision, and for certain purposes, can be treated as isolable, though none are in the strictest sense isolated. The past history of life is a highly complex matter hidden from current observation, whose basic laws

can only be disclosed by chains of inferences. It is therefore proper scientific method to pay the closest possible attention to those aspects of the total history of life which can now, or soon, be subjected to direct observation, analysis, and experimental control. The fact that certain aspects of genomes and of their operation are the result of adaptive selection in the past does not render it any less desirable to study other properties which can be directly correlated with internal factors. One of these latter is the structure of developmental processes as affected by specific mutations, particularly those leading to new successful differentiations. This is rapidly becoming accessible to exact analysis using the empirical and theoretical methods of the various structural sciences.

In fact it is here suggested: 1. That theoretical separation of D.S. from A.S. is already possible over a significant part of the organic realm, though it may be difficult in micro-organisms such as bacteria until the C.C. have been identified. 2. That observational separation is likely to be achieved for many taxa in the coming decades.

The basic features of the proposed theoretical separation may be summarized thus: —

Criterion of Selection. D.S. Conformity of the mutated genotype to the C.C., and adequate closeness to previous type, so that coordinated replication and development are possible. A.S. External adaptive, competitive, and reproductive efficiency.

Scientific Status of these Criteria. D.S. This criterion may soon be susceptible to direct observational confirmation by structural studies, independently of its phylogenetic consequences. For example, if (i) HADORN'S analysis (1948, 1961) of the ontogenetic events caused by lethal genes in insects were supplemented by similar studies of successful mutations, and (ii) the lethal and successful mutations could be shown respectively not to satisfy and to satisfy certain C.C.s, this might be considered to provide a direct confirmation of the operation of D.S. A.S. Adaptive efficiency in the past being beyond direct examination, the only evidence is indirect, from the consequences of such efficiency: differential reproduction shown in population changes inferred from paleontological data, etc.

"Tautology"? D.S. That well-ordered genotypes survive D.S. (in a constant appropriate environment) will become a scientific hypothesis capable of confirmation when (a) the C.C. being known, provide a structural definition of "well-ordered" capable of direct test; and (b) the development of the corresponding genotype can be followed.

A. S. That the fittest survive is meaningful, but quasi-tautological in terms of the available evidence, since past individual fitness cannot be directly investigated, only records of species populations in various periods being preserved.

Evolutionary Change. D.S. Changes permitted by D.S. can occur even in a constant environment or without significant environmental changes, provided the genome is subject to variation (spontaneous or induced mutation, recombination. *etc.*) A. S. Changes permitted by A.S. are associated with changes in the physical and organic environment, including outbreeding, inter-breeding, drift, isolation, *etc.* All major evolutionary changes must have been based on genetic variations permitted by D.S.; A.S. may not always have played an important role, *e.g.*, clumsy animals may survive for long.

Features of selective process. D.S. Operates on the individual organism in all-or-none manner, usually early in development. Permissible mutations may occur most easily and be selected before or during the DNA replication and coherent structured metabolism involved in cell growth before the first division. Result: elimination or survival of developing individual. Some examples (developmental lethals) are already repeatable. A. S. Operates statistically in the history of populations, through hours or millions of years. The primary history is not repeatable. N. B. The developmental selective process has two distinct successive consequences: (i) on the survival of the developing individual; (ii), as a result of (i), on the statistics of the corresponding population. The second effect amounts to a statistical book-keeping of the first, as affected also by A.S., but the statistical structure of a population bears no direct relation to the micro-structural criteria involved in D.S.

Characters preserved by selective process. D.S. Stability and efficiency of replication and internal coordination in an appropriate environment. Also possibly certain secondary, adaptively neutral, characters, such as some coloration, number of plant petals, *etc.*, which may be consequences of structural conditions in the genome. Adaptively clumsy or inefficient types may survive D.S. A. S. New, differentiated or other, phenotypes with adaptively valuable competitive characters (size, strength, speed, mode of reproduction, fecundity, sense organs, brain, *etc.*).

A basic theoretical separation applicable to all species, even to bacteria and other micro-organisms, will only be possible when the C.C. have been identified. But the above contrasts are more than adequate to provide the basis for a provisional separation in several realms of the two classes of

factors. This is already possible, for example, where a protected developmental, *e.g.*, embryonic, phase can be distinguished from a subsequent open phase; where sufficient is already known of the chemical morphology of the earliest form-determining and growth processes; and where evolutionary changes can be studied in a constant environment.

Objection B. However reasonable such arguments may appear, they are premature and lack scientific precision and predictive power. What observational evidence is there for D.S.?

Eliminative D.S., which is well known, implies some degree of permissive D.S. Moreover if the genetic system determines the relative rates of certain kinds of mutations, for which there is evidence, then it must also set restrictions on the effective directions of evolutionary change. These indirect arguments are sufficient to provide a warning of the possible importance of internal factors.

Moreover since 1940 many workers (*e.g.*, STERN, 1943; SPURWAY, 1949, 1960; LIMA-DE-FARIA, 1952, onwards; LANGRIDGE, 1958; SONDLI, 1961; and others less explicitly) have found themselves led to interpret particular genetic observations in terms of the influence of internal factors (such as pre-mutational conditions, genetic control of mutations, mutator genes, genetic and developmental homeostatis, developmental barriers, *etc.*) restricting the possible lines of evolutionary change. For example, LIMA-DE-FARIA (1962) has stressed the importance of the criterion of "compatibility with the system of order which is the chromosome field".

Though it may be difficult to anticipate how a particular perturbation or transformation of the developmental processes will be traced to a specific locus and chromosomal structure, many techniques are already converging on this task, which is crucial to the theory of ontogeny. Within a generation it should be possible to produce selected mutations of known genome structures in particular species and to observe the elimination of some, and the successful operation of others, in the processes of development.

Another line of research which is already leading towards the identification of the C.C. as they affect the genome and its mutations is the statistical study of non-random arrangements in biological macro-molecules. Recent biochemical and theoretical studies (*e.g.*, R. V. ECK, 1961, 1962; H. H. PATTEE, 1961) point to restrictions on the possible sequences in the linear biomolecules expressing specificity. PATTEE considers that there is an important element of order in such macromolecules which is a pre-condition, not a consequence, of adaptive evolution. Certain changes in the order in biomolecules may be

more stable or probable than others. Such constraints form part of the C.C. and studies of coding must ultimately throw light on the C.C. Coding determines a specificity which is not arbitrary, but must satisfy the C.C.

When the C.C. have been partly or wholly identified and when knowledge of the structure of chromosomes and their immediate environment is sufficiently advanced, it may become "possible to predict the class of mutations which is capable of surviving D.S. in a given species in a constant environment" (WHYTE, 1960).

SUMMARY

1. It is likely that internal factors play an important role in restricting the possible avenues of evolutionary change from any starting point. Internal selective processes operating on premutational disturbances, on mutations, and on developmental phases may usefully be separated from the adaptive selection of phenotypes.

2. The precise structural and morphological consequences of internal factors should soon become an isolable problem owing to a) the observational correlation of definite changes in hereditary specificity with particular developmental consequences; and b) the progressive theoretical identification of the coordinative conditions in organisms.

3. Increasing clarity regarding the coordinative conditions should throw light on the "mutational selection rules" and on the differentiative mutations which led to the most important steps in the past history of evolution.

ZUSAMMENFASSUNG

Die Wege der Evolution können sowohl durch innere Auslese der Genotypen während der Entwicklung als auch durch die äussere Darwinische Auslese der Phenotypen bestimmt werden. Seit 1949 haben sich zumindest fünf Forscher (SPURWAY, VON BERTALANFFY, LIMA-DE-FARIA, HALDANE und der Verfasser) mit dieser Möglichkeit befasst. Es ist zur Zeit möglich, zwischen den beiden Arten von Zuchtwahl theoretisch und experimentell zu unterscheiden.

RÉSUMÉ

Les chemins de l'évolution peuvent être déterminés non seulement par la sélection extérieure Darwinienne des phénotypes mais aussi par la sélection intérieure des génotypes pendant le développement. Depuis 1949 aux moins cinq investigateurs (SPURWAY, VON BERTALANFFY, LIMA-DE-FARIA, HALDANE, et l'auteur) en ont considéré la possibilité. Il est possible à présent de faire la distinction entre les deux types de sélection dans la théorie comme dans l'expérience.

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