Developmental Selection of Mutations

Abstract. The direction of evolution may at times be determined by the internal selection of genotypes during development, rather than by the external selection of phenotypes. Biological theory and experiment have reached the point where those concerned with evolutionary problems or with nuclear and cellular organization should consider this possibility.

In studies of the genetic basis of the theory of evolution by natural selection there has been, until recently, little explicit consideration of the possibility that the internal developmental selection of mutations (in contrast to the environmental selection of developed organisms) may sometimes be an important factor in determining the direction of evolutionary change. Some degree of developmental selection of genotypes has occasionally been considered to be probable, and is indeed implicit in the conception of lethal mutations. But the fact that the internal developmental selection of genotypes, rather than the external adaptive selection of phenotypes, may at times be the primary factor determining the direction of evolutionary change has seldom been made explicit (*1*). Though environmental selection is always selection of the ultimate developmental effects of genes, the internal selection of genes and of their earlier effects is a distinct process which merits more consideration than it has yet been given. A line may be drawn between the two at the moment when the developing zygote faces a nonparental environment.

In any structural view of organisms point mutations unrelated to the structure of the organism, or other accidental structural rearrangements, which occur in a highly patterned chromosomal and other neighborhood, will necessarily be subject to a complex and progressive selective process in which the criterion is compatibility with the internal structure and processes of the system, in particular with chromosomal activities. It is widely agreed that in certain respects the genes act as unblending units, and in others as cooperative or "coadaptive" elements in an ordered gene complex which must satisfy certain over-all conditions if an adequately coordinated organism is to result, but little is known regarding these conditions.

The internal selective process may be roughly divided into two phases: (i) some mutations will not adequately conform, at their locus, to the specific ordered molecular structure characterizing the genic system and may therefore be physically or biochemically unstable and be at once eliminated; and (ii) some of those surviving this test will prove less capable (or incapable) of having their activity coordinated within the highly ordered processes of replication, activation, differentiative development, and prefunctional activity, and either they will be modified (by a return mutation or otherwise) in the course of these processes so that they do adequately conform, or, the resulting structures will damage the internal coordination and in severe cases arrest development. Mutations at any locus, to be nonlethal, must possess specific features which, though not yet understood, may play a part in determining the evolutionary process at certain times possibly equal to that of environmental adaptation. "Natural" selection, understood in the full sense, comprises two separable selective processes: developmental selection (where the criterion is internal organizational efficiency permitting continued growth), and environmental selection (dependent on adaptive success, permitting continued life and reproduction). Any phenotype which is adaptively successful must correspond to a genotype which has passed the internal selective process, but that is no reason for neglecting to consider the effects of internal selection, as far as knowledge permits. In much current writing on genetic and evolutionary theory terms such as "natural selection," "adaptive," "favorable," and so forth, are used in a manner which excludes internal developmental selection.

In the view presented here initially haphazard mutations are rapidly sifted, the particular organism choosing what is sufficiently compatible with its existing specific structure. The struggle for survival of mutations begins at the moment mutation occurs. Members of a viable species must be not only adaptively well adjusted, but internally well coordinated, and the latter property is tested first and may, in certain respects or during certain periods, be the more severe restriction on permissible mutations.

The effect of this internal organizational selection of mutations on evolutionary change has received relatively little analysis, probably because until recently it lay outside the scope of biological experiment (*2*) and theory (*3*). But if a prior selective process operates on the mutated genotype, in terms of its compatibility with the highly specific structural processes of development—and it is hard to see how this could fail to be the case on any structural theory of organisms accounting for their coordination—then many arguments concerning evolution by natural selection (gene stability, rates of variation, speciation, macroevolution, and so forth) may have to be reconsidered. The absence of direct evidence for such an effect does not justify its neglect by evolutionary theory, if it is a natural inference from any structural interpretation of organic processes.

The purpose of this note is to invite the attention of specialists to three questions: (i) What evidence exists for developmental selection and what light does the evidence throw on the criteria involved? (ii) What contribution can chemical or other theories of cellular or nuclear organization make to this issue? (iii) Under what circumstances may developmental selection play a decisive role in determining the direction of evolution?

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References and Notes

1. Some relevant references are: H. T. Pledge, *Science Since 1500* (Harper, New York, 1959), p. 226 ("the gene-complex is an 'environment' for mutations in the organism"); I. I. Schmalhausen, *Factors in Evolution* (Blakiston, New York, 1949) (The idea of developmental selection appears to be used, though not made fully explicit); C. H. Waddington, *Strategy of the Genes* (Macmillan, New York, 1957), pp. 65–66 (The possibility of selection acting directly on the mutated genes is considered but dismissed); T. Dobzhansky, *Genetics and the Origin of Species* (Columbia Univ. Press, New York, 1937) (Evolutionary paths may conceivably diverge owing to genetic control of the *directions*, as well as the *rates*, of mutation); J. B. S. Haldane, in *Darwin's Biological Work*, P. R. Bell, Ed. (Cambridge Univ. Press, Cambridge, 1959), p. 147 (Haldane says 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"); ———, *J. Genet.* **56**, 11 (1958); J. H. Woodger, in *The Axiomatic Method*, L. Henkin *et al.*, Eds. (Humanities, New York, 1959), p. 427 (Woodger stresses the importance of random development, as well as random union of the gametes, in obtaining the Mendelian ratios).
2. One of the first observational indications of the internal selection of mutations was reported by Lima-de-Faria [*Chromosoma* **5**, 1 (1952); see p. 53]. See also C. H. Waddington, *Strategy of the Genes*, p. 66, on mutator genes.
3. The possibility of coordinated chromosomal action, which is connected with the present argument, has been discussed by Schmalhausen in *Factors in Evolution*, by R. B. Goldschmidt in *Theoretical Genetics* (Univ. of Calif. Press, Berkeley, 1955), p. 184–186, and 487, and by Waddington in *Strategy of the Genes*. But conceptions such as "autoregulation," "canalization of development," "systemic mutations," and so forth, might be better defined by explicit consideration of developmental selection.

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Atropine-like Actions of Muscarine Isomers

Abstract. Molecular pharmacology of muscarine isomers has been studied in the rat intestine and frog heart. The significance of the peculiar finding of atropine-like action of some of the isomers is discussed.

The activity of a drug is mainly characterized by affinity and intrinsic activity (*1*). The intrinsic activity, representing the ability of a drug to produce an effect, is also a measure of the