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ABSTRACT: Constitutivity can be brought about by genetic fixation of one of two (or more) possible responses to an environmental stimulus so that the manifested response is independent of external environmental stimuli. It has been argued that the appearance of constitutivity cannot play a creative rôle in evolution because it decreases the flexibility of the organism's responses to the environment. I want to show that constitutivity can be brought about by the integration of previously unintegrated systems and their functional association. It is suggested that evolutionary innovations brought about in this way may be particularly relevant to the evolution of behaviour.

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Genocopy is not a widely used biological concept. Indeed, its definition is not to be found in King's Dictionary of Genetics. The definition, as used for example by Lorenz, is the other pole of the definition of phenocopy. While phenocopy is defined as a phenotypic character produced by environmental stimuli (stress or some change in the "normal" environment) which mimics a phenotypic character produced by genetic mutation, genocopy is the very opposite. I shall define genocopy as a hereditary character whose manifestation is unregulated by environmental stimuli and which mimics a previously "tunable" hereditary character, i.e. a character whose manifestation was evoked by an environmental stimulus. At one time the existence of this phenomenon was considered by some biologists to be proof of the inheritance of acquired characters in the Lamarckian sense. However, as a result of Waddington's theoretical and experimental contributions, the acquisition of acquired characters now rests on the relatively solid basis of selection, and does not involve any Lamarckian relationship between the environmental stimulus and the change in genetic material which is visualized as primarily functional (activation or inactivation of genes) and brought about by directional selection rather than directional mutation.

For Waddington the unit of selection was the phenotype, which is determined by particular combinations of genes and the environmental influences responsible for the activation of these combinations of genes. Since only that which is expressed is under selection pressure, an organism possessing an allele A will be selected if it contributes to the adaptability of the specific combination of genes expressed in a new environment. The frequency of such an allele in a population living in the new environment will increase, as will the frequency of other alleles of different genes which take part in and contribute to the adaptive advantage of the new character. Through selection the most "fit" combination of genes (that which responds with maximum effectiveness to the new stimulus, or that which "foresees" the stimulus) will become fixed in the population. This is Waddington's "genetic assimilation" through the process of canalization. In this way a phenotypic trait may become assimilated, provided there is sufficient genetic variability in the population, and provided the selection process is constant in character and lasts long enough. Experimental examples of non-adaptive genetic assimilation were provided by Waddington (1,2) and a possible example of adaptive genetic assimilation might have been, as Waddington (2) and Gould (4) suggested, Kammerer's famous midwife toads. Piaget's snails (3) may provide a naturally occurring example of genetic assimilation (2).

The progress made in molecular biology, and especially the progress in understanding regulation at the various molecular levels (DNA, transcription, processing, translation, protein products, etc.), has made it possible to understand some of the mechanisms underlying such phenomena. The classical work of Jacob and Monod

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(5) on the lac operon is probably most relevant in this context. Wild type E.coli K-12 synthesise Lac products in the presence of an external inducer, usually lactose. The inducer combines with a repressor protein produced by a gene from the same lac operon, and in so doing releases the operator gene and allows the transcription of the whole operon. Jacob and Monod also showed that mutations in the operator gene or in the gene producing the repressor protein result in constitutive mutants. In these mutants the synthesis of Lac products does not depend on the availability of the external inducer. Such constitutive mutants can be thought of as genocopies of the inducible wild-type, since they exhibit a fixed response, unregulated by an environmental stimulus.

The elucidation of the repression/derepression mechanism in bacteria opened up some new evolutionary perspectives. In the absence of glucose, E.coli K-12 uses lactose for growth, the first step in lactose catabolism being performed by the product of lacZ, β-galactosidase. P.H.Clarke (6) has discussed work that shows how when a deletion of lacZ occurs, the existence of a gene ebg coding for a second β-galactosidase can be revealed. This gene was not detected before the deletion occurred because in the wild type the activity of its gene product was insignificant. To obtain the lactose-positive phenotype in the absence of lacZ, two mutations are necessary — one regulatory mutation (ebgR $\longrightarrow$ ebgR$^-$) which renders the previously undetected operon constitutive, and a second mutation in the structural gene ebgA (ebgA^o $\longrightarrow$ ebgA$^+$) to produce an enzyme with increased rates of lactose hydrolysis. The combination of ebgR$^-$ (constitutivity) with ebgA$^+$ (increased rate of lactose hydrolysis) results in sufficient enzyme activity for growth, while in the wild type the in vivo activity is below the threshold value. It was also possible to obtain from E.coli K-12, with a lacZ deletion, a family of mutants with new growth phenotypes. All of these carried mutations in both ebgR and ebgA and included strains able to utilize lactose, methyl-galactoside, lactulose and lactobionate. This example shows that in some special circumstances (in this case lacZ deletion) constitutivity is a necessary condition for revealing the full potential of an enzyme for utilizing a large range of sugars.

One common criticsm which is advanced against the fixation of a genocopy ("constitutivity") as an evolutionary event building up complexity, is that it decreases the flexibility of the organism's responses. Constitutivity may sometimes be considered as a special case of adaptive specialization. The critics believe it to have limited evolutionary significance because this type of specialization involves a decrease in the flexibility of an already existing trait rather than the acquisition of a new specialized competence. It is argued that before such fixation the organism was capable of two (or more) responses. After fixation it is capable of only one. "To the extent that a wolf can be trained to live with man, the domestic dog becomes a genocopy* of the trained wolf. In this respect, the so-called genocopy corresponds to a decrease in the genetic potentialities of the organism ... the genocopy would not correspond to the acquisition of a new competence, but to a loss of genetic potentialities ... it is easy to conceive of the genocopy as deriving from a polymorphic type as a result of a loss (or an inactivation) of the genes that determine the other phenotypes and as a result of the 'constitutive' (unregulated by the environment) expressions of the remaining genes" (Changeux, p.196 in ref.7). Dunchin too reasons in a similar way:- in a genocopy "one was witnessing a simple degeneration of the initial type which had lost regulatory aptitudes that allowed it to change its phenotype according to the environment and had only retained one aspect" (Dunchin, p.359 in ref.7).

Although this criticism is somewhat oversimplified as the example of the ebg

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*The author responsible for this quotation, as well as the one responsible for the next quotation, used the term "phenocopy" rather than genocopy. The reason for this was that the criticism was addressed at Piaget who had stressed the potential evolutionary importance of genocopies, but in doing so had made the mistake of using the term "phenocopy", and the critics used the term in his way. (Piaget could not answer their criticism, but he stuck to his intuition with characteristic stubbornness!). I have used "genocopy" in the quotation to avoid unnecessary confusion.

mutations in E.coli K-12 indicated, this reasoning must certainly apply in some situations, where the loss of "flexibility of responses" may be uncompensated. But this is certainly not the only alternative. It is possible to imagine a situation where the loss in genetic potential is compensated for by a greater increase in complexity. I will compare two alternative ways in which genocopies could be produced:- (a) a loss of flexibility of responses to external environmental stimuli with no compensation; (b) a loss of flexibility of responses to external environmental stimuli compensated by the production of functional interdependence of two systems. In both cases only one basic genetic difference is required to bring about the effect.

A: Let R,o,a,b,c constitute an operon system (operon OP-A); a, b and c are structural genes, o is the operator gene, and R is the regulator gene. Initially, depending on the environmental conditions, two phenotypes are possible:-

(i) When R is producing a functional repressor, it represses the operator o, and genes a, b and c are inactive. This happens in the absence of an external inducer. The phenotypic result of such repression in character Ch-1.

(ii) In the presence of an external inducer, the inducer combines with the regulator gene R's product. The operator o is released, and the now activated genes a, b and c produce the character Ch-2.

It is obvious that if, because of a mutation in either R, or o, or both, the product of R cannot combine with o, one character only (Ch-2) can be produced; in this case the loss of genetic flexibility is uncompensated (provided, of course, that no far-reaching pleiotropic effects are involved).

B: Consider the same operon (OP-A), but now the operon is controlled by an internal inducer. This internal inducer is capable of combining with the product of R, and releasing the operator with the consequent manifestation of Ch-2, now unregulated by the external environment. The new internal inducer could be a metabolic product of another, hitherto unrelated, metabolic pathway. It is now capable of combining with the product of R, either because of a mutation in R ($R \longrightarrow R_2$, with R_2's product capable of combining with the internal inducer), or because of a mutation in the unrelated operon (OP-B) resulting in a higher production of the metabolic product which acts as an internal inducer. In both cases the formation of the complex "internal inducer-repressor" results in a constitutive change — only Ch-2 will now be manifested. In this case too, we witness the loss of some genetic flexibility, but here a new functional association between two previously unrelated operons has occurred.

The emergence of this latter type of constitutivity could be brought about by natural selection. In environmental conditions favouring constitutivity, selection of genotypes containing a particular allele of R and particular alleles of the gene or genes producing the internal inducer might occur. If it does occur, then the result may be thought of as one of the simplest cases of Waddington's "genetic assimilation", involving as it does the selection of only a few (possibly only two) alleles.

What is the evolutionary significance of such a new association between two, previously unrelated, operons? There are several interesting possibilities. Providing the selection pressure which was responsible in the first place for the fixation of the Ch-2 phenotype is not altered significantly, the internal inducer now becomes indispensable. This fact can exert selection pressure on the activity of the whole Op-B operon (e.g. an increase in the production of all Op-B products). The increase in the production of all Op-B products can in its turn have many potentially important effects, like, for example, the ability to use a greater range of substrates by Op-B's gene products. The chain of events can be further extended, or altered, but the basic idea is that the interdependence of previously independent operons is a background for entirely new selection pressures. When Lorenz described most cases of phylogenetic ritualization (as shown for example in the duck species) he said that "a new (hereditary) pattern arises, whose form copies that of a behaviour pattern which is variable and which is caused by several independent motivations" (8). In other words, a fixed ritualized behaviour pattern in one species is thought to have evolved from patterns of behaviour which allowed flexibility of responses to specific stimuli in other species. The complex ritualized patterns of behaviour are the product of the integration of simpler and more variable patterns of behaviour.

This is a good example of the potential of genocopy-fixation for increasing complexity (more complex behaviour in this case) in the course of evolution.

The evolution of such interdependence is probably a rare event, as a maladaptive disruption of the organism's "inner-equilibrium" is often to be expected. Nevertheless, it seems to me, that potentially such interdependence might be responsible for important innovations of evolutionary significance. As behaviour is particularly susceptible to external-environmental changes, it may be of the utmost importance in the evolution of behaviour.

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