Canalization, Genetic Assimilation and Preadaptation: A Quantitative Genetic Model

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ABSTRACT

We propose a mathematical model to analyze the evolution of canalization for a trait under stabilizing selection, where each individual in the population is randomly exposed to different environmental conditions, independently of its genotype. Without canalization, our trait (*primary phenotype*) is affected by both genetic variation and environmental perturbations (*morphogenic environment*). Selection of the trait depends on individually varying environmental conditions (*selecting environment*). Assuming no plasticity initially, morphogenic effects are not correlated with the direction of selection in individual environments. Under quite plausible assumptions we show that natural selection favors a system of canalization that tends to repress deviations from the phenotype that is optimal in the most common selecting environment. However, many experimental results, dating back to Waddington and others, indicate that natural canalization systems may fail under extreme environments. While this can be explained as an impossibility of the system to cope with extreme morphogenic pressure, we show that a canalization system that tends to be inactivated in extreme environments is even more advantageous than rigid canalization. Moreover, once this adaptive canalization is established, the resulting evolution of primary phenotype enables substantial preadaptation to permanent environmental changes resembling extreme niches of the previous environment.

THE concept of *genetic assimilation* was introduced by Waddington (1953, 1961) to highlight the remarkable outcome of several artificial selection experiments in which an environmentally induced phenotypic modification became expressed even in the absence of the external stimulus that was initially necessary to induce it. For example, when pupae from a laboratory population of wild-type *Drosophila melanogaster* were exposed to heat shock, some of the emerging adults exhibited a gap in the posterior crossveins of the wings that is not normally observed in untreated flies (Waddington 1952, 1953). After some generations of selection, when only these abnormal individuals were allowed to breed, the proportion of adults with broken crossveins induced by heat shock at the pupal stage was raised above 90% and, moreover, a small proportion of individuals were crossveinless even among flies that had not been exposed to temperature treatment. If artificial selection was then continued by breeding the adults that had developed the abnormality without heat shock, the frequency of crossveinless individuals among untreated flies became very high, reaching 100% in some lines. Genetic assimilation has been repeatedly demonstrated in Drosophila for a variety of morphological traits and environmental stresses (*e.g.*, Waddington 1956; Bateman 1959a,b).

As explained by Waddington, the development of crossveins and other apparently very stable morphological traits can be influenced by environmental disturbances above a certain threshold of intensity, but individuals from wild-type populations have a threshold so high that only an unusually strong stimulus, such as a heat shock, can effectively induce a modified expression. According to Waddington's explanation, the phenotypic uniformity generally observed in these traits can easily coexist with the abundant genetic variability demonstrated by artificial selection in assimilation experiments. Although different genotypes available in a population are sensitive to different threshold values of external stimuli, phenotypic variation does not arise if all of them have too high a threshold to be affected by the disturbances prevailing in the usual environment. However, when an exceptionally severe disturbance occurs, the subpopulation of individuals in which a phenotypic change is induced is necessarily enriched for the most sensitive genotypes, which provide the material for artificial selection.

The peculiar pattern of interaction between genetic and environmental variation that underlies the expression of crossveins, and of other traits that can be similarly subject to assimilation, was described by Waddington using the concept of *genetic canalization* (Waddington 1940). When the expression of a trait is well canalized,

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most genetic and environmental variation has no, or very little effect on the phenotype, so that a population remains phenotypically uniform even if it contains substantial genetic heterogeneity, or is exposed to wide fluctuations of the environment. For this reason, it is expected that canalization is tighter for those traits that most crucially contribute to fitness (Waddington 1941; Schmalhausen 1949). Phenotypic effects, however, can be produced if individuals are subject to severe perturbations and, in this respect, genetic and environmental factors are considered largely equivalent from the point of view of canalization (Waddington 1961). Thus a mutation at a major locus and an external shock can produce identical changes on a trait, as demonstrated by phenocopies. The distinctive aspect of canalization, which makes assimilation possible (Waddington 1942, 1961), is the fact that, once the expression of a trait is modified by a sufficiently severe perturbation, the effects of minor factors that are normally repressed also become exposed, resulting in a substantial increase of phenotypic variation in the population.

The nature and the genetic bases of canalization have been studied in detail by Rendel and by several other authors (Rendel 1959; Rendel and Sheldon 1960; also, *e.g.*, Dun and Fraser 1958, 1959; Milkman 1960, 1961). A thorough review and careful interpretation of the results was given by Rendel (1967). Instead of an environmental stress as a tool to uncover hidden variation for bristle number in the scutellum of *D. melanogaster*, Rendel used a recessive mutant allele, sc^1, of the sex-linked locus *scute*. In flies of the wild type the number of bristles is essentially fixed at four, variant individuals being exceedingly rare. In unselected mutant stocks, however, the average number of bristles is about 1.0 for females (sc^1/sc^1) and 0.5 for males (sc^1) and variability is quite high as, for example, only 33% of females have one bristle. Most of this increased variability, however, is not intrinsic to the mutant allele. In fact, after a population in which sc^1 and the wild-type allele (+) were segregating was subject to selection for a high number of bristles, the sc^1/sc^1 genotype reached a mean of almost four bristles and variation was substantially decreased (*e.g.*, only 12% of individuals differed from the mean), while in the $+/+$ genotype, where the mean had become about eight, variation was increased dramatically (ranging from four to twelve bristles). Clearly, in these populations development of scutellar bristles is subject to powerful canalization to prevent variation around four bristles and it is only when it is forced to deviate far from this target that underlying variation is expressed. Moreover, the target of canalization on the phenotypic scale is under genetic control and can be displaced by selection. This was demonstrated by Rendel and Sheldon (1960) who, by artificial selection for low variability in a population homozygous for sc^1, were successful in shifting the canalization to around two bristles. Canalization of the unstable expression of mutant traits was also obtained in several other artificial selection experiments in Drosophila (Maynard Smith and Sondhi 1960; Waddington 1960) and in the house mouse (Kindred 1967).

These and several other results obtained by different authors can be nicely explained by a model proposed by Rendel (1967) to describe a simple system of regulation leading to canalization. According to this model, a canalized trait is determined by four kinds of factors: (i) one or a few major genes, (ii) a number of minor genes, (iii) environmental factors and (iv) the regulatory system. Both major and minor genes, subject to environmental effects, are responsible for the production of a morphogenic substance of some kind. The *primary phenotype*, which Rendel calls Make, is the total amount of this substance that would be produced in the absence of regulation, while the expressed phenotype is proportional to the amount of substance that actually becomes available as a result of the interaction of the primary determinants with the regulatory system. The contributions to Make of major genes, minor genes and environment are additive. The regulatory system functions as a repressor of the major genes. As long as the level of Make is not larger than the amount, M_0, required to obtain the desired expression of the trait, repression is silent and the resulting trait is proportional to Make. When, instead, the level of Make begins exceeding M_0, repression of the major genes is activated so as to keep the actual production of morphogenic substance as close as possible to M_0. Since regulation only operates on the major genes, this production cannot be depressed below that part of Make that is caused by minor genes and environment. In addition, a certain portion of the contribution of major genes might also be nonregulatable. Thus, if the part of Make that cannot be regulated is itself larger than M_0, the expression of the trait will exceed the desired level and will increase as Make increases. It is therefore clear that regulation is effective only as long as Make is contained within the *canalization range* $R = [M_0, M_0 + m]$, where m denotes the regulatable portion of major genes' contribution to Make. If the major genes are selected for optimal production, as in the wild type, Make usually falls in the canalization range and all moderate variations because of minor genes and environment are damped out. If the wild-type alleles of a major locus are replaced by mutations, or major external disturbances intervene, Make may go out of range and underlying variation is exposed.

Since canalization promotes the accumulation and preservation of a large store of hidden genetic variation, which could be exposed and rapidly exploited by natural selection in case of sufficiently drastic environmental changes, Rendel (1967, pp. 148–157) considered that it must have important effects on the mode and rate of evolution. In fact, he argued that in the course of evolution long phases of phenotypic stasis, during which canalization systems are redirected and refined, should

alternate with rapid shifts when the phenotype migrates to a new adaptive peak, a view that anticipates the more recent theory of *punctuated equilibria* (Eldredge 1971; Eldredge and Gould 1972). Basically the same mode of evolution was predicted by Schmalhausen (1949) in his theory of stabilizing selection, which introduced genetic concepts closely related to canalization, and by Waddington (1957, 1961) who, in particular, maintained that genetic assimilation plays an important evolutionary role by generating substantial phenotypic innovations and accelerating adaptation to foreign environments. In fact, according to his view, as soon as a population faces a sudden but lasting alteration of the environment, or colonizes an unfamiliar habitat, a number of phenotypic changes are likely to emerge, directly induced by stressful external conditions. Some of these changes, being more suitable to the present environment than the current wild type, will help the population to survive through the critical situation and at the same time will provide natural selection with genetic variation that the process of assimilation can rapidly use to stabilize and improve the new adaptation.

Waddington's theory has been refuted by Williams (1966) who, without denying the reality of genetic assimilation, argued strongly against the significance of its role in the process of adaptation. Missing crossveins and other anatomical anomalies utilized in assimilation experiments reflect disruptions of development caused by exceptionally severe external perturbations. It is only through the artificial selection imposed by the experimental design that assimilation of these characters can be successful in the laboratory. As maintained by Williams, phenotypic modifications of this kind, which are a direct result of environmental interferences to which the species is not prepared to respond, are likely to be disadaptive under most circumstances and, even if there were a condition in which any of these would be adaptive, we should expect it to be quite different from the condition that is specifically required to induce the given variation directly. Thus, if certain extreme situations become recurrent or permanent, any phenotypic change that they could cause would be eliminated by natural selection rather than assimilated. Phenotypic disruptions directly induced by the environment are, therefore, not expected to provide useful material for any evolutionary progress.

Williams also discussed the role of assimilation in relation to a very different form of phenotype-environment interaction, which generally is referred to as (adaptive) *plasticity*. This occurs in the many cases in which an organism is able to respond to changing conditions of the environment with specific modifications of certain traits, in a way that is appropriate to preserve the quality of its vital activities. This kind of phenotypic reaction to external stimuli is obviously a sophisticated adaptation to variability of the environment, which can only be achieved through a complex and slow process of natural selection (Via and Lande 1985; de Jong 1990, 1995; Scheiner and Lyman 1991; Gomulkiewicz and Kirkpatrick 1992; Gavrilets and Scheiner 1993; Zhivotovsky *et al.* 1996). Once a trait has evolved plasticity in this way, it could become a target of genetic assimilation whenever some appropriate varying factor of the environment becomes more stable. In fact, in the new situation, there is a selective advantage for the genotypes that more reliably express the particular state of the trait that is most adequate to the level of the external factor that now prevails.

Assimilation in a plastic trait of *D. melanogaster* has been demonstrated by Waddington (1959) and, more recently, by te Velde *et al.* (1988) in experiments concerning the morphology of anal papillae, a larval organ that is involved in the regulation of osmotic pressure of internal fluids. When larvae are reared in a medium with salinity sufficiently high to cause substantial mortality, their anal papillae become, relative to body size, slightly larger than those of larvae grown in normal media. The macroscopic change of these organs is associated with adaptive modifications in the ultrastructure of their membranes (te Velde *et al.* 1988), which apparently function in the regulation of ion exchange. In Waddington's experiments, a number of populations were maintained under conditions of high salt concentration for several generations. No artificial selection was applied, so that the populations were subject only to natural selection, driven mainly by the larval mortality caused by the elevated salinity of the medium. As a result, at the end of the experiments the selected strains were better adapted to high salt concentrations, since larval mortality had decreased in comparison to the initial populations. In addition, significant genetic assimilation had occurred because larvae from the selected strains retained enlarged anal papillae even when reared in a medium of normal salinity.

Thus, just as Williams pointed out, when genetic assimilation is applied to a plastic trait, the result is the loss of a flexible response, which is replaced by a stereotyped expression of the trait, a condition that in many respects can be regarded as a more elementary mode of adaptation. Hence, from his analysis Williams could conclude that genetic assimilation is not, as Waddington maintained, a major factor in the emergence of new adaptations, and, when it plays a role in evolution it has, in fact, the contrary effect of simplifying and restricting the range of response of plastic traits.

Canalization is a widely recognized and well-documented phenomenon that continues to be a topic of lively research. Stearns and Kawecki (1994), analyzing the extent of canalization of various life-history traits in *D. melanogaster*, have found that, as predicted by Waddington, canalization is more effective for traits to which fitness is more sensitive. The same kind of data have been used by Stearns *et al.* (1995) to demonstrate that the patterns of canalization against genetic and

environmental disturbances are closely parallel, suggesting that a single regulatory mechanism keeps in check both sources of variation, in agreement with Rendel's model. On the theoretical side, Gavrilets and Hastings (1994) have proposed a quantitative-genetic model of canalization against environmental disturbances in a trait subject to selection. They show that when selection on the trait is stabilizing, tighter canalization readily evolves in a way that could preserve, or even increase, the heritability of the trait, a feature that has been observed in experiments with artificial stabilizing selection. The model of Wagner *et al.* (1997) also analyzes evolution of canalization, but takes into account both environmental and genetic perturbations. These recent studies are just the latest issues in a long tradition of mathematical research on selection for the regulation of phenotypic variability. Particularly interesting in this broader context are the results of Levins (1965) and of Slatkin and Lande (1976), concerning a quantitative trait subject to optimizing selection in a fluctuating environment, such that the optimal phenotype varies form one generation to the other. Though these two works differ in their modeling approach and in the quantitative details of the results, they basically agree in the main prediction that, if fluctuations of the environment are moderate enough, selection would favor any repression of phenotypic variation (*e.g.*, through canalization), but, if the environment fluctuates widely, selection favors instead genetic systems that preserve or, maybe, amplify the expression of phenotypic variations. In the recent literature there is a growing interest in *fluctuating asymmetry*, namely the occurrence of random differences between left and right in traits that normally have bilateral symmetry. In the past, there has been disagreement as to whether variability of this type truly indicates poor canalization (*e.g.*, Mather 1953; Reeve 1960; Waddington 1961; Kindred 1967; Rendel 1967, pp. 134–135), but now this property is widely used as a tool to evaluate, even at the individual level, the quality of canalizing systems, and the extent of genetic and environmental stresses on development (Mackay 1980; Maynard Smith *et al.* 1985; Parsons 1992). A variety of estimation procedures and criteria to distinguish it from other forms of asymmetry has been developed (Palmer and Strobeck 1986). Clarke and McKenzie (1987) used fluctuating asymmetry to evaluate the impact on developmental stability of insecticide resistance genes, which spread in wild populations of the Australian sheep blowfly, *Lucilia cuprina*, after introduction of insecticides. They found that newly established resistance alleles induce an increase of fluctuating asymmetry in bristle counts and other traits. However, if an allele has been maintained in a population for a sufficiently long time by the continued use of the insecticide that selected for resistance, levels of fluctuating asymmetry are as low as in flies of the susceptible strains. These effects are not intrinsic to specific resistance alleles but are a property of the genetic background. In fact, if a resistance allele from a wild strain with low asymmetry is transferred to the extraneous genetic background of a susceptible strain, asymmetry increases again. These results confirm the notion that variation of well canalized traits can be exposed by major genetic perturbations of any kind and, supplementing older results on artificial selection, provide evidence that canalization systems are modified by natural selection. Arguing from the experimental evidence that in several cases females have a preference for males with symmetrical ornaments, some authors (Møller 1992; Møller and Pomiankowski 1993) have proposed the hypothesis that females may use fluctuating asymmetry or, in general, the degree of regularity of elaborate secondary sexual characters, as a reliable cue to the genetic quality of their potential mates. Thus, according to this hypothesis, canalization might be the actual target of female preference and the basis of sexual selection.

Given that canalization is a rather general property of adaptive traits, it is important to consider again the theoretical question of whether the large unexpressed store of genetic variation that it can preserve could play a significant role in the evolution of new adaptations. To be valid, a positive answer should overcome the flaw that Williams found in Waddington's assimilation hypothesis. In this article we develop a quantitative model to analyze the evolution of canalization of a genetically determined trait subject to stabilizing natural selection. When not canalized, expression of the trait is affected by random environmental perturbations. Variability of the environment also influences the pattern of selection, in that in each particular environment, to which an individual is randomly assigned, a different trait-value would be optimal. Taking into account the reservations of Williams, we assume that the morphogenic influence of a deviation of the environment from normal does not necessarily lead to a phenotype that is better adapted to this specific deviation. We take into consideration, though, the possibility that activation or inactivation of the canalization system itself, like any other physiological feature, might be affected by some general environmental factor such as stress, irrespective of the selective advantage or disadvantage of the resulting phenotype. If so, it is natural to further assume that the way the environment affects the canalization system is controlled by genes, that these genes are subject to variations and that such genetic variations are also subject to natural selection.

In the framework of this structure we find that, under the same conditions that enable the evolution of a rigid canalization system as envisaged and studied by Rendel, a more flexible, so to say *adaptive* system of canalization is always advantageous for the individual organism. We show next that the very development of such an adaptive canalization system elicits, in turn, further evolution of the selected trait. This evolution is such that, in the long

term, the population acquires a substantial degree of preadaptation to possible sudden, permanent changes of the environment that resemble some rare environmental condition of old. These processes may account for long-term evolutionary modes such as punctuated evolution and, possibly, atavism. As it turns out, though, short-term testable predictions of the suggested adaptive canalization model are, in most though not in all aspects, very much similar to predictions drawn from the model of Rendel. While both models seem to fit equally well the bulk of experimental results of Waddington and others, we attempt to point out some crucial differences between the two sets of predictions, and, thus, some possible experimental designs that may tell one from the other.

MORPHOGENIC AND SELECTING FACTORS OF THE ENVIRONMENT: A QUANTITATIVE FORMULATION OF RENDEL'S THEORY OF CANALIZATION

We assume that the phenotype P of an individual is determined by both its genotype G and the environment E it is exposed to. The viability of this same individual, in turn, depends on its phenotype and, again, on the environment it finds itself in. Thus, the viability $w_E(G)$ of an individual of a given genotype G depends on the environment E in two different ways: first the environment affects the phenotype of the individual, then it imposes a selection pressure on the reshaped phenotype, say

$$w_E(G) = w(E, P(G,E)). \tag{1}$$

If the environment affects the phenotype in a way that makes it more suitable to survive within it, then one speaks of (adaptive) plasticity. For example, sun tan, resulting from exposure to ultraviolet radiation, provides the organism with protection against further exposure. Plasticity enables the same genotype to survive under a wide variety of environmental conditions. But, as pointed out by Williams (1966), this complex phenomenon is unlikely to occur by mere chance and should, therefore, be recognized as a result of natural selection. Thus, excluding the special condition of adaptive plasticity, the environmental factors (*e.g.*, prenatal shock, early wound damage, deficiency or excess of a nutrient) that affect a certain trait (*e.g.*, body weight) in most cases are likely to be different from those (*e.g.*, intensity of mate competition) that impose direct selection on the same trait. In such cases it is worthwhile to make explicit the distinction between environmental factors that directly affect a specific phenotypic trait u, and those that impose selection on it. Hence we will refer to the ensemble of environmental factors of the first sort as the *morphogenic environment* (E_M) and to environmental factors of the latter sort as the *selecting environment* (E_S). By making such a distinction one can rewrite (1) as

$$w_E(G) = w(E_S, P(G,E_M)). \tag{2}$$

Our intention in this work is to investigate, quantitatively, the possibility that canalization might lead to preadaptation, as predicted by Waddington (1957, 1961), by taking into account the criticism raised by Williams (1966). Hence, we make the assumption that the phenotypic changes, induced by the morphogenic component of the environment are, at least initially, independent of the adaptive changes that would be favored by natural selection under the same environmental conditions. We refer to this as *Williams' requirement.* Note that this requirement does not contradict the common empirical observation of adaptive phenotypic response to environmental pressure (as is the case with the response of human skin to sun radiation). It only requires that such a phenotypic response, if it occurs systematically, must, inevitably, be the result of a long process of natural selection. In fact, the evolution of a phenotypic adaptive response appears to be one possible result of the model suggested in this work, rather than an assumption superimposed on it as a given rule of nature.

We assume a population in which each individual is exposed at random to somewhat different environmental conditions. We concentrate on a single quantitative phenotypic trait, which is affected by many genetic and environmental factors, mostly independent or weakly dependent on each other. We can, therefore, adopt the quite common assumption of a normal distribution of the trait in question, with initial variance

$$\sigma^2 = \sigma^2(P(G,E_M)) = \sigma_G^2 + \sigma_E^2, \tag{3}$$

where σ_G^2 and σ_E^2 stand for the genetic and for the *morphogenic* environmental components of the phenotypic variance, respectively. Likewise we assume that the phenotype, determined by the random components G and E_M is exposed to the random component E_S of the *selecting* environment. Dealing with a single, quantitative phenotypic trait, it is convenient to rescale E_S by identifying all possible environmental situations where fitness is maximized by the same phenotypic value, v. We refer to this ensemble as the v-selecting environment. It is easy to see that with this rescaling of the selecting environment, Williams' requirement simply states that E_M and E_S are independent.

Using this one-dimensional rescaling of the selecting environment, we now denote by $w(u,v)$ the viability of the phenotype u in the selecting environment v. For any given value v of the selecting environment we know that $w(u,v)$, as a function of the individual's phenotype u, is maximized at $u = v$. For simplicity, we assume Gaussian selection, so that

$$w(u,v) = w(v,v)e^{-(u-v)2/2\gamma 2}, \tag{4}$$

where the constant $1/\gamma$ measures the intensity of selection on the phenotypes. Assuming further that the contribution of environment v to the surviving adults of

each generation has a Gaussian distribution, and that v is scale-adjusted to the standard mean zero and variance one, we can readily get the a priori viability of an individual of phenotype u:

$$w(u) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} e^{-(u-v)^2/2\gamma^2} e^{-v^2/2} dv = \frac{\gamma}{\sqrt{\gamma^2 + 1}} e^{-u^2/2(\gamma^2+1)}. \quad (5)$$

Because $w(u)$ is a decreasing function of the distance u^2 between the value of the trait, u, and the mean of the selecting environment, $Ev = 0$, we see that the overall selection on the trait is stabilizing in spite of the variable environment. Hence, any genetic factor that reduces the phenotypic deviation $|u|$ of its carrier from the average of the selecting environment is likely to be selected for. Thus, in the first place, selection on the loci that directly affect the trait will make its mean, Eu, evolve toward the optimal value, $Ev = 0$, and will reduce the genetic component σ_G^2 of the phenotypic variance to a minimum. Yet, this sort of selection alone leaves intact the environmental component σ_E^2 of the phenotypic variance and cannot eliminate a residuum of genetic variance due to mutation-selection balance. Thus, in the second place, natural selection is likely to favor modifier genes that, through some regulatory effect, can further reduce the phenotypic deviations of their carriers from the optimum. The first possible mechanism of this sort, suggested by Fisher (1928), is that of modifier genes inducing dominance of the wild type [for some critique on Fisher's theory for the evolution of dominance, however, see Wright (1934) and Rendel (1967); for alternative models see Haldane (1930), Muller (1932), and Plunkett (1933)]. Canalization is an alternative mechanism that is effective on deviations of both genetic and environmental origin (Waddington 1952, 1953; Rendel 1967; Stearns *et al.* 1995).

In its most general form, canalization to the optimal value $Ev = 0$ can be characterized by any mapping from the original phenotypic trait u to a modified expression $\theta(u)$, where for all u, $\theta^2(u) \le u^2$. In this case it is convenient to distinguish between what we now refer to as the *primary phenotype*, u, and its canalized expression, $\theta(u)$. Thus, in the model of Rendel,

$$\theta(u) = \begin{cases} u + R & \text{if } u < -R \\ 0 & \text{if } -R \le u \le R \\ u - R & \text{if } u > R, \end{cases}$$

where R is the range of canalization. A tacit assumption in this model is that the canalization modifier itself is unable to respond to signals from the environment. With this assumption, it immediately follows from (5) that, for any primary trait value u, natural selection will operate to flatten the graph $\theta(u)$ of the phenotypic expression, thereby producing canalization over as wide a range as allowed by the physiological constraints at the primary loci [see Wagner *et al.* (1997), for a detailed analysis of factors that may set a limit to this range]. The existence of mutant forms in nature and, more so, the empirical findings concerning the exposure of mutant forms under extreme stress conditions are, thus, explained by Waddington and Rendel on the mere technical basis of physiological limitations, which are the same for all organisms within the population and, therefore, are not, by themselves, responsive to natural selection.

In the next section we see that a finite range of canalization, quite distinct but analogous to that observed by Rendel, can, in fact, evolve as a result of natural selection rather than being imposed on the organism by mere physiological restrictions. More specifically, we see that inactivation of the canalizing system under conditions of extreme stress (stress being defined in terms of the selecting environment) is, under plausible conditions, selectively advantageous for the individual.

ADAPTIVE INACTIVATION OF THE CANALIZING SYSTEM UNDER ENVIRONMENTAL STRESS

It is not difficult to imagine specific situations in which inactivation of the canalizing system would be advantageous to the organism. Indeed, such a situation occurs, quite trivially, when both the primary phenotype, u, and the selecting environment, v, are far from the average zero and close to each other. The ability of an organism to "assess" such a situation and to inactivate the canalizing system accordingly must represent, if it exists, a very advanced stage in the course of evolution and may be a first step in the evolution of plasticity. In this work, however, we concentrate on the much more primitive ability of the organism to assess only the general stress under which it finds itself and to activate or inactivate the canalizing system accordingly. The evolution of such an ability appears inevitable if we assume that: (i) the activity of the canalizing system, like that of most other systems within the living organism, is affected by environmental stress; and (ii) there is some genetic variation among individuals in the population with respect to the effects of stress on their canalizing system. By endorsing these assumptions, we simply wish to apply to the canalizing system itself the same hypotheses that in Rendel's model are assumed for an ordinary trait that evolves canalization.

In a population which is canalized around zero, a signal for inactivation of the canalizing system can be just the value v of the selecting environment. Notice, though, that under Williams' assumption of independence of the selecting and morphogenic components of the environment, this value cannot possibly provide the organism with any information about its own primary phenotype, which may deviate from v even more than its canalized phenotype does. In fact, one can easily see that, choosing u and v independently at random,

$E(v-u)^2$, the expected square distance of v from the primary phenotype u, is always larger than Ev^2, the expected square distance of v from the canalized phenotypic value zero. This means that, under any environmental condition v, inactivation of the canalizing system is likely to create more nonadaptive "monsters" than organisms which are better adapted to the specific selecting environment v. Yet we shall see that, nevertheless, when v is large enough in absolute value, *i.e.*, under harsh enough environmental stress, inactivation of the canalizing system is favored by natural selection.

To compare the fitness of a random, canalized organism with that of a noncanalized one, when exposed to the same selecting environment v, we integrate both quantities over all primary phenotypic values u. More generally, we denote by $w_{\theta(u)}(v)$ the average fitness, in the selecting environment v, of a random individual whose canalizing system transfers the primary phenotypic trait u into some function $\theta(u)$ of u. Recalling Equations 3 and 4, we get

$$w_{\theta(u)}(v) = \frac{w(v,v)}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{+\infty} e^{-[\theta(u)-v]^2/2\gamma^2} e^{-u^2/2\sigma^2} du.$$

In the case $\theta(u) = 0$ of full canalization to the mean, (6) becomes

$$w_0(v) = w(v,v)\ e^{-v^2/2\gamma^2}. \tag{7}$$

In the case $\theta(u) = u$ of no canalization, it becomes

$$w_u(v) = \frac{w(v,v)}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{+\infty} e^{-(u-v)^2/2\gamma^2} e^{-u^2/2\sigma^2} du$$

$$= \frac{\gamma w(v,v)}{\sqrt{\sigma^2+\gamma^2}} e^{-v^2/2(\sigma^2+\gamma^2)}. \tag{8}$$

Hence, inactivation of the canalizing system in the selecting environment v is advantageous if and only if the value v satisfies the inequality $w_u(v) > w_0(v)$. Employing (7) and (8) [as long as $w(v,v) > 0$], this inequality becomes

$$\frac{w_u^2(v)}{w_0^2(v)} = \frac{\gamma^2}{\sigma^2+\gamma^2} e^{\sigma^2 v^2/\gamma^2(\sigma^2+\gamma^2)} > 1, \tag{9}$$

independently of $w(v,v)$. Inequality (9) can be written, more conveniently

$$v^2 > \frac{\gamma^2(\sigma^2+\gamma^2)}{\sigma^2} \ln\left(1 + \frac{\sigma^2}{\gamma^2}\right) = \hat{v}^2, \tag{10}$$

say. Hence, there is an average selective advantage for inactivation of the canalizing system whenever conditions of the selecting environment are harsh enough, *i.e.*, if $v^2 > \hat{v}^2$, where $\hat{v} = \hat{v}(\gamma, \sigma)$. Employing (10), one can readily verify that

$$\gamma^2 < \hat{v}^2 < \gamma^2 + \sigma^2; \tag{11}$$

namely, canalization is always advantageous when $v^2 < \gamma^2$ and disadvantageous when $v^2 > \gamma^2 + \sigma^2$. A canalization system that, through natural selection, has acquired the property of being inactivated whenever the selective environment is sufficiently harsh, *e.g.*, as specified by Equation 10, will be called adaptive.

A generalization of (10) is obtained if, for any selecting environment v, we allow for partial inactivation of the canalizing system, namely, if we allow for a partial instead of a full shift of the phenotypic trait to the mean, say $\theta(u) = \theta_v u$, $0 \le \theta_v \le 1$. We employ (6) to get the fitness $w_\theta(v)$ of a random individual with partial canalization $\theta(u) = \theta u$ under the selecting environment v:

$$w_\theta(v) = \frac{w(v,v)}{\sqrt{2\pi\sigma^2}} \int_{-\infty}^{+\infty} e^{-(\theta u - v)^2/2\gamma^2} e^{-u^2/2\sigma^2} du$$

$$= \frac{\gamma w(v,v)}{\sqrt{\theta^2\sigma^2+\gamma^2}} e^{-v^2/2(\theta^2\sigma^2+\gamma^2)}. \tag{12}$$

Hence,

$$\frac{\partial w_\theta(v)}{\partial \theta} = c'[v^2 - (\theta^2\sigma^2 + \gamma^2)], \tag{13}$$

where $c' > 0$ for all θ and v. Thus, as a result we get the following

Corollary.(i) *If $v^2 < \gamma^2$, then the derivative* (13) *is always negative, which means that the average fitness $w_\theta(v)$ of an individual with a canalizing system θu, when exposed to the selecting environment v, is maximized at $\theta = \theta_v = 0$. Hence, within this range of the selecting environment, natural selection will operate in favor of full canalization.*

(ii) *If $v^2 > \gamma^2 + \sigma^2$, on the other hand, the derivative* (13) *is positive for all $\theta \le 1$, which means that the average fitness of an individual, exposed to such a selecting environment is maximized at $\theta = \theta_v = 1$. Hence, within this range of the selecting environment, natural selection will favor complete inactivation of the canalizing system.*

(iii) *Finally, in the range $\gamma^2 \le v^2 \le \gamma^2 + \sigma^2$ of "intermediate" selecting environments, natural selection will operate in favor of partial inactivation of the canalizing system, because, for any v in this range, $w_\theta(v)$ is maximized by*

$$\theta_v^2 = \left(\frac{v^2 - \gamma^2}{\sigma^2}\right),$$

which lies then between 0 and 1.

It is clear that once adaptive canalization has evolved, or even before this as long as the prevailing canalization system is susceptible to inactivation by certain environments, the assumption (2) that the selective environment does not have morphogenic effects no longer applies to the expressed phenotype, because now the state of the selective environment determines whether canalization is going to be active or not. But, notice that, as we anticipated in the previous section and in agreement with William's requirement, it is only through natural selection that this phenotypic response to the selective environment becomes adaptive. Adaptive canalization, in fact, could be viewed as a very rough and primitive

kind of plasticity, which, as we have shown, can evolve from an initial state described by condition (2). On the other hand, this condition continues to be valid as applied to the primary phenotype even after adaptive canalization has evolved.

COEVOLUTION OF THE CANALIZING SYSTEM AND THE PRIMARY PHENOTYPE

So far, we have concentrated our analysis on the evolution of modifier loci that produce and regulate canalization. We have seen that, as long as no canalization system exists, natural selection would operate to reduce mutations at major loci that cause deviations from the optimum. Such mutations can only remain in the population at low frequency, due to mutation-selection balance, and, together with variations of the morphogenic environment, contribute to the variance σ^2 of the primary phenotype. The situation remains qualitatively the same once a canalizing system that is insensitive to the selecting environment has evolved. The only difference is that, now, selection against mutations of the major loci is much weaker than before, because actual expression of most variations of the primary phenotype is suppressed by canalization. The consequence of this is simply an increase of the primary phenotypic variance σ^2, since these mutations will reach, under mutation-selection balance, a substantially higher frequency than before.

The situation is different, however, once an adaptive canalizing system, reacting to signals from the selecting environment, has evolved. In this case we know that the average fitness of an adaptively canalized individual is higher than that of a fully canalized one, where averaging is over all selecting environments, v, and primary phenotypes, u. It follows that, averaging over all v's, there must be some values of u that are selectively advantageous over $u = 0$, so that there is some selective advantage to at least small enough deviations of the primary phenotype from the mean $u = 0$, in either direction. In fact, such deviations, while normally suppressed by canalization, are exposed only under extreme selecting conditions, when there is an advantage to certain deviations (in the appropriate direction) from the mean phenotype. On the other hand, it can be shown easily that, not surprisingly, natural selection should always operate against too large deviations from the mean.

We, therefore, expect that, once an adaptive canalization system has evolved, at least certain deviations from the mean will be positively selected, rather than maintained by a mutation-selection balance. Moreover, from the symmetric structure of the model it appears that these deviations will be equally advantageous when either to the left or to the right of the mean zero. One possible consequence of this fact might be a fast build-up of a rather high primary genetic variance around zero, which is strictly selected for, rather than just neutrally protected by canalization.

It has been suggested by Rendel (1967), in a view different from that of Fisher (1928), that the common phenomenon of dominance can be explained by the canalization of the relatively small deviations of the primary phenotypes of heterozygotes. As he has maintained, cases in which the phenotypic expression of a deviating mutant is actually observed are, quite often, those of the relatively more drastic homozygote effect. Experiments, demonstrating the exposure, under rare conditions, of a phenotypic effect in otherwise repressed heterozygotes substantiate this possibility (see Rendel 1967 for references). This explanation, however, faces a theoretical difficulty because it requires that in a vast majority of cases the boundary of the morphogenic range of canalization just happens to fall exactly between the primary phenotype of the heterozygote and that of the mutant homozygote, a situation which is quite unlikely because the mutant homozygote effect can range widely. Yet, the introduction, in addition, of an adaptive range of canalization in the selecting environment may resolve this difficulty. Those mutant alleles whose heterozygote effect exceeds the morphogenic range of canalization are normally selected against and, therefore, rarely observed. Others may be either neutral under normal conditions, or recessive in the sense that only the homozygote effect exceeds the morphogenic range of canalization and is, therefore, selected against. But, as it has been argued above, the heterozygote may have a slight selective advantage in the latter case because it expresses itself only under conditions of extreme environmental stress, where it may be advantageous on the average. We therefore might observe a strong statistical bias toward this situation of recessive deviations from the mean.

This is one possible example of how the establishment of an adaptive canalization system may affect the selection forces that operate on primary phenotypes. But we know, on the other hand, that the exact character of the adaptive canalization system depends heavily on the distribution of the primary phenotype, more specifically on its variance and on the assumption that it is symmetrically distributed around the environmental optimum, $Ev = 0$. Thus the crucial question to be answered is how the two systems, primary phenotype and canalization, evolve together.

To deal with this kind of question, a slightly more general perspective than that taken so far is required. We now consider a population of genetically identical individuals, all homozygous for a specific combination of alleles of major genes and canalization modifiers that determines a mean primary phenotype y and a *canalization policy* λ. For each individual, the value, u, of the primary phenotype is drawn from the distribution

$$p(u,y) = \frac{1}{\sqrt{2\pi\sigma^2}}\, e^{-(u-y)^2/2\sigma^2}, \qquad (14)$$

which, as before, is normal and has fixed variance σ^2,

but the mean, y, may vary depending on the genotype at the major loci. However, the phenotype actually expressed, $\theta(u,v)$, depends on the particular selecting environment, v, to which the individual is exposed, in a way that is dictated by the canalization policy λ. Namely, confining our consideration to "deterministic" policies, we assume that, for each given environment v, $\lambda = \lambda(v)$ takes one of the two values, zero and one, such that

$$\lambda(v) = \begin{cases} 0 & \text{then } \theta(u,v) = 0 \\ 1 & \text{then } \theta(u,v) = u, \end{cases} \tag{15}$$

so that the expression of u is canalized to the mean selecting environment, $Ev = 0$, in the environments v where the policy λ takes the value zero, while canalization is inactivated whenever λ takes the value one. Recall, now, that the fitness of an individual expressing phenotype u in selecting environment v is $w(u,v)$ (Equation 4), and that the contribution of environment v to surviving adults of each generation is given by the Gaussian distribution with mean zero and variance one. We, therefore, find that the fitness, $W(\lambda,y)$, of a genotype that codes for the pair (λ,y) is given by

$$W(\lambda,y) = \int_{-\infty}^{+\infty} [(1 - \lambda(v))s_0(y,v) + \lambda(v)s_1(y,v)]\, e^{-v^2/2}\, dv, \tag{16}$$

where

$$s_0(y,v) = \int_{-\infty}^{+\infty} \frac{w(0,v)}{w(v,v)}\, p(u,y)du = e^{-v^2/2\gamma^2} \tag{17}$$

and

$$s_1(y,v) = \int_{-\infty}^{+\infty} \frac{w(u,v)}{w(v,v)}\, p(u,y)du = \frac{\gamma}{\sqrt{\sigma^2 + \gamma^2}}\, e^{-(v-y)^2/2(\sigma^2+\gamma^2)} \tag{18}$$

represent the fitness in environment v of a genotype coding for a mean primary phenotype y, given that its specific policy respectively activates or suppresses canalization when exposed to v.

We now look for an unbeatable pair (or pairs) (λ,y) (see Hamilton 1967), namely a pair that satisfies, at least locally,

$$W(\lambda,y) > W(\lambda',y') \quad \text{for all } \{\lambda',y'\} \neq \{\lambda,y\}. \tag{19}$$

To establish that long-term evolution, by mutations of small effect and selection, does lead to the establishment of such a pair, see Matessi and Di Pasquale (1996). To determine the solutions of (19), we can first find a policy $\hat{\lambda}_y$ that, for any given y, maximizes $W(\lambda,y)$ with respect to λ, and then find a mean primary phenotype y° that maximizes $W(\hat{\lambda}_y,y)$ with respect to y. From the definition of the canalization policy $\hat{\lambda}_y$ one concludes immediately that

$$\hat{\lambda}_y(v) = \begin{cases} 0 & \text{if } s_0(y,v) \geq s_1(y,v) \\ 1 & \text{if } s_0(y,v) < s_1(y,v). \end{cases} \tag{20}$$

Thus, to identify explicitly the optimal canalization policy $\hat{\lambda}_y$ for each y, we need only determine the values v of the selecting environment over which

$$s_0(y,v) \geq s_1(y,v). \tag{21}$$

In fact, inequality (21) determines the optimal range of adaptive canalization, given the mean primary phenotype y. Employing (17) and (18), inequality (21) can be written as

$$\ln\left(\frac{\gamma^2 + \sigma^2}{\gamma^2}\right) \geq \frac{v^2}{\gamma^2} - \frac{(v-y)^2}{\gamma^2 + \sigma^2}. \tag{22}$$

For any given value of y, the right-hand side of (22) is a quadratic form of v with a nonpositive value at $v = 0$. Hence, inequalities (21) and (22) are satisfied over the range of values $v_-(y) \leq v \leq v_+(y)$ of the selecting environment v, where $v_-(y) < 0$ and $v_+(y) > 0$ are the two roots of (22) as an equality. We, thus, get

$$\hat{\lambda}_y(v) = \begin{cases} 0 & \text{for } v_-(y) \leq v \leq v_+(y) \\ 1 & \text{for } v < v_-(y) \text{ or } v_+(y) > v. \end{cases} \tag{23}$$

Obviously, when the mean primary phenotype is equal to zero, (22) readily yields $-v_-(0) = v_+(0) = \hat{v}$, where $\hat{v} > 0$, as given by (10), is the canalization threshold that is optimal when the distribution of primary phenotypes is centered on the mean zero of the selecting environment. For a general value of y, (22) yields $-v_-(-y) = v_+(y)$. One can also see that $v_+(y)$ tends to $+\infty$ [and, thus, $v_-(y)$ tends to $-\infty$] as y tends to $\pm\infty$. Finally, one can see that if $y > 0$, then $-v_-(y) > v_+(y)$. This means that, quite as expected, canalization is more likely to persist when deviations of the selecting environment from its mean are in the opposite direction of that of the mean primary phenotype.

Now, given the optimal canalization policy for any mean primary phenotype, the optimal values y° of the mean primary phenotype can be determined by maximizing the fitness $W(\hat{\lambda}_y,y)$ with respect to y. Following (16–18), we can write this fitness function as

$$\begin{aligned} \Phi(y) = W(\hat{\lambda}_y,y) = {} & \frac{1}{\sqrt{2\pi}} \int_{v_-(y)}^{v_+(y)} e^{-v^2/2}\, e^{-v^2/2\gamma^2}\, dv \\ & + \frac{\gamma}{\sqrt{2\pi(\sigma^2 + \gamma^2)}} \left[\int_{-\infty}^{v_-(y)} e^{-v^2/2}\, e^{-(v-\gamma)^2/2(\sigma^2+\gamma^2)}\, dv \right. \\ & \left. + \int_{v_+(y)}^{+\infty} e^{-v^2/2} e^{-(v-y)^2/2(\sigma^2+\gamma^2)}\, dv \right]. \end{aligned} \tag{24}$$

From the symmetry of the model it immediately follows that $\Phi(y) = \Phi(-y)$. Hence, it will be sufficient to study the behavior of $\Phi(y)$ for $0 \leq y < \infty$. Employing the fact that $v_+(y)$ tends to $+\infty$ and $v_-(y)$ tends to $-\infty$ as y tends to $+\infty$, (24) readily yields the limit result

$$\Phi(\infty) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{+\infty} e^{-v^2/2\gamma^2}\, e^{-v^2/2}\, dv, \tag{25}$$

which is the fitness of a genotype with mean primary

phenotype equal to zero and unrestricted canalization. Because we know already that, when $y = 0$, the best policy, $\hat{\lambda}_0$, restricts canalization to the finite interval $[-\hat{v},\hat{v}]$, and since $W(\hat{\lambda}_0,0) = \Phi(0)$, we conclude immediately that

$$\Phi(0) > \Phi(\infty). \tag{26}$$

A maximal value of $\Phi(y)$ must, therefore, be obtained either at $y = 0$ or at two finite values $\pm y^\circ$, where $y^\circ > 0$. For $y = 0$ it follows from (24) that

$$\Phi'(0) = 0 \tag{27}$$

and

$$\Phi''(0) = \frac{2\gamma}{\sqrt{2\pi(\sigma^2 + \gamma^2)^3}} \times \left[\frac{\gamma^2}{\sigma^2}\hat{v}\, e^{-((1+\sigma^2+\gamma^2)/2(\sigma^2+\gamma^2))\hat{v}^2} + \int_{\hat{v}}^{+\infty} \left(\frac{v^2}{\sigma^2 + \gamma^2} - 1\right) e^{-((1+\sigma^2+\gamma^2)/2(\sigma^2+\gamma^2))v^2}\, dv\right], \tag{28}$$

where the optimal canalization threshold $\hat{v}$ is a function of σ^2 and γ^2 as given by (10). Hence, $y = 0$ is a stationary point of $\Phi(y)$, and to know whether it corresponds to a (local) minimum or maximum of fitness we have to evaluate the sign of $\Phi''(0)$.

By straightforward calculation it can be shown that for any fixed value of γ, if σ^2 is large enough, the right-hand side of (28) is negative and $\Phi(y)$ obtains a local maximum at $y = 0$. We, thus, conclude that in the situation where the variance of the primary phenotype is sufficiently large, as compared to the variance of the selecting environment (which, by defnition, is one), natural selection would prevent any shifting of the mean primary phenotype away from the mean of the selecting environment. In the same way it can be shown that if the variance of the primary phenotype is sufficiently small, as compared to the variance of the selecting environment, $\Phi(y)$ obtains a local minimum at $y = 0$, which implies that average fitness is maximized at any of two finite values $\pm y^\circ$, where $y^\circ > 0$. We, therefore, get the interesting result that in this situation, selection on the major genes will indeed favor a shift of the mean primary phenotype either to the right or to the left of the mean of the selecting environment, the choice between the two equilibria, y° and $-y^\circ$, being essentially determined by random historical events.

We see now that in any of these two situations, a canalization system, selected to optimize individual success under variable environmental conditions, enables the population to cope with, and efficiently adapt itself to, a variety of drastic environmental changes. The nature of this sort of preadaptation, however, will be different in the two situations.

DIRECTED PREADAPTATION, NONDIRECTED PREADAPTATION AND ATAVISM

Until now we have been concerned with a population in which individuals were subject to varied, random environmental conditions, independently of each other. We have assumed, though, that the entire environment is fixed. By this we mean that the distribution of environmental conditions to which the various individuals in the population are exposed does not change from one generation to the next. We have seen that under such conditions, an adaptive canalization system is expected to evolve, which will inactivate itself in case of an unusual environmental stress. When this is the case, it is expected that, at any generation, only a relatively small proportion of the population will be exposed to such stressful conditions and, consequently, will reveal its otherwise suppressed primary phenotypic deviations from the central, canalized trait-value.

The situation is different in the case of a drastic change of the entire environment or, say, a catastrophe. In this case, all (or most) individuals in the population will be exposed to an environmental stress which may be drastic enough to inactivate their canalization system, with the resulting exposure of the entire distribution of the primary phenotypic deviations from the central, canalized trait. Following Williams' assumption (and, apparently, contrary to Waddington), we do not assume any correlation between the selecting demand and the morphogenic effect (on the primary phenotype) of the environment. Yet, the basic result of our analysis is that the distribution of phenotypes, exposed by the environmental change, is strongly enriched with traits that were advantageous, each in some niche of the pre-catastrophe environment. Moreover, as has already been maintained by Wright (1931, 1956), the new environmental conditions imposed on the population are most likely (though not certain) to somehow resemble those prevailing in rare niches before the catastrophe. If this is the case, the population would therefore present a substantial degree of *preadaptation*, that would take it into a process of *punctuated evolution* (*e.g.*, Eldredge 1971; Eldredge and Gould 1972; see also Rendel 1967, pp. 148–157) caused by fast selection in favor of a specific exposed phenotype that is already adjusted to environmental conditions quite similar to those presented by the new environment. As follows from our analysis, a substantial genetic component of the suppressed phenotypic deviations from the canalized trait is maintained in the population by the environmentally sensitive canalization system. Hence, selection in favor of the preadapted phenotype enables a fast process of assimilation, comparable to that observed by Waddington and others in an artificial laboratory setting. Note, however, that this fast process of phenotypic adaptation to the new environment is likely to be followed by an equally important, slow, hidden process of build-

up of a new canalizing system, adjusted to the new environment, with a subsequent accumulation of phenotypically suppressed genetic variance (see Rendel 1967, pp. 148–157). It is only this hidden process that may provide the population with potential preadaptation to a variety of possible new environmental changes.

As we have seen in the previous section, long exposure of the population to the same variation of environmental conditions can produce two sorts of preadaptation: (i) a symmetric range of canalization with a relatively high level of suppressed phenotypic variance, which may provide the population with rough preadaptation to any drastic change within the continuum of the existing selecting environments; (ii) a deviation of the mean primary phenotype in a specific direction along this continuum, which is likely to provide the population with even better ability to cope with drastic changes in this specific, seemingly premeditated direction, but with poor ability to cope with changes in the other direction. In this case one can speak of preadaptation in the narrow sense. We have, further, seen that in this case the choice of the predetermined direction of preadaptation may depend on mere chance, but it may be as well the result of a historical cause. A likely candidate for such a cause may be a remnant of asymmetry in the distribution of primary phenotypes because of the presence of genotypes, which were advantageous in a previously common environment. If such genes have not fully disappeared from the population when a new canalizing system is built up, and if, indeed, the conditions of the selecting environment are such as to allow for the evolution of a biased canalizing system, it can be predicted that a biased preadaptation in the direction of the old environment is more likely to be established. In this event one may speak of *atavism.*

SOME SUGGESTIONS FOR THE EXPERIMENTAL DISTINCTION BETWEEN THE MORPHOGENIC AND THE SELECTING ENVIRONMENT MODELS OF CANALIZATION

The selecting environment model of canalization presented in this work is not intended to replace Rendel's morphogenic environment model but, instead, to add to it another dimension, not to be ignored as well, namely that of natural selection. In other words, we propose to extend Rendel's one-dimensional range of canalization to a bi-dimensional range, $\mathcal{R} = \{(u,v) : u \in [-R,R];\ v \in [v_-,v_+]\}$, such that the phenotypic variance, which, as a norm, is suppressed in $\mathcal{R}$, can be exposed under any of the two, generally rare, situations: (i) the morphogenic situation, in which the combined effect of morphogenic environment and mutant genes exceeds the biological limitation of the canalizing suppressor ($u \notin [-R,R]$); and (ii) the adaptive situation, when the entire canalizing system is inactivated under an extreme environmental stress ($v \notin [v_-,v_+]$).

Experimentally, it may be hard to distinguish between occurrences of these two situations and, indeed, many experimental findings of Waddington and others, mentioned above, appear to fit each of them equally well. This is so because, even though the morphogenic and the selecting *effects* on the phenotype are independent of each other, any specific environmental factor could be active in both respects. In fact, the environmental conditions, such as heat shock, high salinity, etc., chosen by Waddington and other workers to be artificially imposed on their experimental populations, were regarded only in respect to their morphogenic effect. Yet, without exception, they were all extreme stress conditions as well. Conversely, it is most likely that any extreme stress condition should have some direct morphogenic effect on the organism. Hence, it is possible that the phenotypic deviations manifested in some of these experiments resulted from adaptive inactivation of the canalizing system under extreme stress conditions. On the other hand, there is no doubt that certain experiments provide a strong if indirect evidence of direct morphogenic effects. For example, the fact that exposure of pupae of *D. melanogaster* to heat shock drastically increases the frequency of crossveinless individuals among adult flies, has been quite convincingly explained by Milkman (1960–1962; see also Rendel 1967) on the basis of a deficiency of an enzyme, the production of which is inhibited by heat. That such a morphogenic effect can be added to that of some mutant genes, is demonstrated by Waddington's experiments of genetic assimilation of this trait through artificial selection.

Although it appears that in most cases a single experiment is very unlikely to distinguish between direct morphogenic effects (morphogenic environment hypothesis) and adaptive inactivation of canalization (selective enviroment hypothesis), we believe that a finer distinction may be obtained by an appropriate set of experiments in which the intensity of a single, one-dimensional environmental factor is repeatedly increased from one experiment to the other. In this case, the predictions of the two hypotheses will be different from each other in two crucial aspects.

The variety of phenotypic deviations manifested by the entire set of experiments: In the morphogenic environment hypothesis, we expect that, during the entire set of experiments, phenotypic deviations will be manifested in only one or, at the most, a few specific traits which are directly affected by the particular morphogenic environmental factor in question.

In the selecting environment hypothesis, on the other hand, one can expect the exposure of phenotypic deviations in a wide variety of canalized traits, all triggered by the same, ever increasing environmental stress signal. Yet, deviations in different kinds of traits may reveal themselves, gradually, at different levels of environmen-

tal stress, as they may be under the control of adaptive canalization ranges of different sizes.

The intensity of any single phenotypic deviation manifested through the set of experiments: In the morphogenic environment hypothesis, because the environment is supposed to create, rather than simply expose phenotypic variants, we expect to observe an intensification of phenotypic deviations as the intensity of the morphogenic factor in question is gradually increased. Moreover, in this case it is also likely that intensification of the same morphogenic factor, which initially has produced the phenotypic deviation in the more powerful mutant genotypes, will gradually extend its effect to weaker ones, down to the wild type and beyond, at least in some cases, so as to affect a gradually increasing proportion of the experimental population, and eventually the totality, or a large majority of it.

In the selecting environment hypothesis, on the other hand, since the environment is, then, supposed to just uncover, rather than create variation, an increase in the intensity of the environmental stress (although likely to expose ever new sorts of phenotypic abnormalities) is not expected to intensify those phenotypic deviations which have been already uncovered. Nor can one expect an increase in the frequency of an exposed phenotypic deviation of any given sort beyond the frequency of mutant genotypes responsible for it, regardless of how intense the environmental stress may grow.

We, therefore, hope that a new set of experiments will be able to throw more light on the question of whether the manifestation of deviating phenotypes under specific stress conditions is because of the direct morphogenic effect of this environment or is because of its indirect effect of inactivating the canalizing system. As we have seen, distinguishing between these two possibilities may have a crucial bearing on our understanding of the process of long-term evolution.

DISCUSSION

Our point of departure in this work has been Rendel's (1967) theory of a limited morphogenic range of canalization. This theory was the first to provide a full physiological explanation, compatible with Mendel's laws of genetic heritability, of the phenomena of canalization and assimilation, observed in a number of experiments executed by Waddington (1940, 1953, 1956, 1960, 1961), Bateman (1959a,b), Milkman (1960, 1961, 1962) and others, as well as by Rendel himself (1959, 1967; see also Rendel and Sheldon 1960; Rendel *et al.* 1965). Rendel's theory does not directly resort to evolutionary arguments, yet it involves several tacit assumptions about the environment in which a canalizing system could have evolved. First, it assumes that different individuals in the population are exposed, during their life spans, to different environmental conditions, so that a random morphogenic effect of the environment generally adds itself to that of genetic mutations. An equally important assumption is that of an average selective advantage endowed to some mean-valued phenotype (stabilizing selection), where the average, in this case, is taken over all possible environmental conditions under which the organism can find itself. Apparently, this assumption is not universally true—there are various selection forces, *e.g.*, frequency dependent selection, that lead to the establishment of phenotypic polymorphism, a situation that, indeed, does not allow for the evolution of canalization.

Conditions for the evolution of a canalizing system with a limited morphogenic range of canalization, as suggested by Rendel, have been demonstrated in a quantitative model. In the development of the model we have taken over what we refer to as Williams' requirement (Williams 1966), namely that phenotypic modifications, induced by the morphogenic effect of the environment (in addition to those resulting from random genetic mutation), are initially independent of the selecting requirements of the same environment. This assumption means that organisms are not intrinsically endowed with a Lamarkian ability to adjust themselves to the requirements of the environment, but that such an ability, namely adaptive plasticity, if and when it exists, has evolved, like any other adaptive feature, as a result of natural selection.

Further analysis of the selective forces inevitably operating under such conditions, however, led us to some new predictions concerning the emergence of *adaptive inactivation* of the canalizing system. More specifically, it has been shown that, although under these conditions canalization is always favored by natural selection when averaged over all environmental situations, it is not so favored under specific situations of extreme environmental stress. It has been shown, moreover, that in such situations, it is selectively advantageous for the organism to inactivate its canalizing system, thus uncovering all its hidden deviations from the canalized mean phenotype. Quite surprisingly, though, it is shown that even in such a situation, most phenotypic deviations uncovered prove to be even less viable than the canalized wild type. Yet the selective advantage of the inactivation of the canalizing system under extreme stress can be explained by the fact that the only phenotypes with any substantial survival probability are, under such conditions, those few which, just by chance, happen to deviate in the "appropriate" direction with respect to the selecting environment. We have calculated the exact range of conditions of the selecting environment under which an adaptive canalizing system should operate. The exact limits of this range are shown to be determined by the variance of the selecting environment, by the intensity of selection and by the variance of hidden phenotypic deviations from the canalized mean.

Demonstrating the selective advantage of an observed phenomenon in natural populations does not necessar-

ily prove it to be the cause rather than a by-product of natural selection. A suggested mechanism of selection may not always be biologically feasible, or else there might not be an evolutionarily feasible route leading to it. Yet, the collapse of a biological system under conditions of extreme stress is a common phenomenon in nature even when selected against. The envisaged collapse of such a system when favored by natural selection is, thus, by no means a farfetched hypothesis. Moreover, a rather crucial assumption in the theory of Rendel is that virtually any quantitative trait is subject to modifying effects both of the environment and of random genetic mutations. We do not see any reason why the canalizing system itself should be excluded from this general rule and, thus, could not be molded by natural selection, a possibility ignored by the original model of Rendel.

The emergence of adaptive canalization, as predicted in our model, combines in a single genetic system two kinds of adaptations that the models of Levins (1965) and of Slatkin and Lande (1976) predict as distinct alternatives evolving in two different types of environment: (i) suppression of phenotypic variation if the environment, and the corresponding optimal trait value, are constant or fluctuate weakly in time; and (ii) full expression or even amplification of phenotypic variation if temporal fluctuations are wide enough. In our model the environment remains constant in time but is, so to speak, heterogeneous "in space" since each individual is placed at random in a niche with a different optimal phenotype; we predict that phenotypic variation is suppressed in the common niches but fully exposed in the extreme niches.

As we have discussed, direct natural selection for the inactivation of the canalizing system under extreme stress conditions can provide an adaptive explanation of the empirical phenomena alternatively explained by Rendel on the basis of physiological or biochemical limitations of the canalizing system to cope with extreme morphogenic agents. Indeed, as we have seen, inevitably such agents also impose, on the target population, extreme stress conditions which, as predicted by the adaptive model, would cause the inactivation of the canalization system. However, the selecting environment model of canalization, suggested in this work, does not preclude Rendel's morphogenic environment model and, therefore, is not intended to replace it but, instead, to add to it a complementary dimension of natural selection. We have proposed some suggestions for an experimental design which might help to distinguish between the two models of canalization.

The addition of the adaptive dimension to Rendel's structure of a canalizing system, turns out to be necessary for the understanding of another role played by canalization in respect to long-term evolution: providing the canalized population with the indispensable combination of phenotypic homeostasis on the one hand, and requisite genetic variance necessary for fast (punctuated) adaptation to an important class of environmental changes, on the other hand. More specifically, a crucial aspect of the selecting environment model of canalization concerns its effect on the accumulation of partly suppressed genes for deviations from the canalized wild type. A limited range of canalization within the morphogenic space, as suggested by Rendel, only mitigates selection against such genes by partly suppressing their effect, which remains deleterious on the average. Instead, as we have shown, once an adaptive range of canalization within the selecting environment has evolved, at least small enough deviations from the canalized phenotype will be positively selected, rather than being simply maintained in mutation-selection balance. This analytic result is intuitively explained by the fact that such deviations, being under normal conditions suppressed by canalization and, hence, neutral, are only exposed to natural selection in the case of extreme stress conditions in which, as we have shown, they are advantageous on average. Since the optimal range of canalization within the selecting environment depends, in turn, on the distribution of primary (partly hidden) variations, we show that coevolution of genes for the primary phenotype and those controlling the adaptive range of canalization will end up with one of the two following evolutionarily stable situations: (1) When the variance of the selecting environment is relatively small, as compared to that of the primary phenotype, a symmetric adaptive range of canalization evolves, under the cover of which a high-variance, more or less symmetric distribution of potential deviations is maintained. (2) When the variance of the selecting environment is relatively high, as compared to that of the primary phenotype, the distribution in the population of the primary, repressed variations evolves a bias to one side of the canalized, expressed phenotype. The range of canalization becomes correspondingly asymmetric, with its larger radius of activity extending to the opposite side. The choice of the direction of asymmetry, in this case, depends on either random or historical factors. This apparently strange result can be understood as if in this case, evidently, being "prepared" to cope well with at least a part of the possible difficult situations was a better strategy than being prepared to cope badly with all of them.

In both cases (though in a somehow different manner), the accumulation of genes for potential deviations from the present environmental mean has, inevitably, a crucial effect on the long-term course of evolution much (though not completely) in line with the predictions of Waddington. Thus, assume that a population, having been for a long time adjusted to the same variable environment, is suddenly exposed to a drastic and persistent change of the environmental conditions. In this case it is predicted by the selecting environment canalization model, much in agreement with the predictions of Waddington (1957, 1959, 1961; see also Schmalhausen 1949; Rendel 1967), that the prevailing canali-

zation system is likely to become inactivated so that the hitherto mostly hidden genetic variance in the population is exposed to natural selection. In such a case, however, Waddington apparently expected the new environment to somehow encourage the appearance of new morphs which are already preadapted to it, which could then undergo a quick process of genetic assimilation through natural selection favoring these novel traits. As we have seen, the crucial difficulty in this evolutionary approach is the need to explain the necessary predesigned ability of organisms to react adaptively to environmental pressure. As has been mentioned by Williams (1966), this very ability, if and when it exists, must represent a higher level of adaptation than just the resulting quick establishment of a specific phenotype best adapted to the new environment.

A crucial contribution of the selecting environment canalization model to a possibly new theory of evolution by assimilation, thus, lies in its prediction that even without an intrinsic drive of the organism to respond phenotypically in an adaptive manner to environmental pressure, the phenotypes uncovered by the inactivation of the canalizing system are not expected to distribute at random. Instead, one expects a strong enrichment of their distribution in favor of phenotypes which, even before, have been advantageous at least in some rare niches of the environment in which they have evolved. Thus, if conditions imposed by the new environment resemble those prevailing in some rare niche of the old, although most of the uncovered phenotypic variance is bound to be nonadaptive, some of the exposed deviations will be preadapted in the direction of the new environment. When the adaptive range of canalization is symmetric, the population is expected to possess a relatively weak preadaptation to environmental changes in any direction. In the case of an asymmetric range of canalization, our model predicts more efficient preadaptation to environmental changes in one specific direction. In this case one may speak of preadaptation in the narrow sense. In either case it is expected, much in agreement with ideas put forward by Schmalhausen (1949) and Rendel (1967), that the observed fast evolutionary process of selection for the establishment of the uncovered, preadapted genotypes will be followed by a hidden, much slower process, during which a new canalizing system is built up, allowing for the accumulation of mostly suppressed deviations from the newly established mean phenotype. Only at the end of such a process will the population become preadapted to further, drastic changes of the environment. The observed process of evolution, in this case, is expected to reveal a sequence of sharp, almost discontinuous jumps with long intervals among them. This prediction is therefore quite in line with the observed paleontological phenomenon named by Eldredge and Gould (1972; see also Eldredge 1971) as *punctuated equilibria.*

Note that when an asymmetric canalizing system is established, the direction of the asymmetry may well depend on historical factors. A likely candidate among these may be the initial existence in the population of genotypes adapted to the previously common environmental conditions. If such genotypes have not fully disappeared from the population when a new canalizing system is built up, it can be expected that a biased preadaptation in the direction of the old environment is likely to be established. In this case one may speak of *atavism.*

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