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CHAPTER 14

Environmentally Contingent Variation: Phenotypic Plasticity and Norms of Reaction

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Variation

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INTRODUCTION

Environmentally influenced variation in phenotypic expression or *phenotypic plasticity* is a fundamental property of organisms with consequences for developmental and ecological genetics, evolutionary biology, population and community ecology, conservation biology, and medicine (Lewontin, 1985; Stearns, 1989; Scheiner, 1993; Schlichting and Pigliucci, 1998; Tollrian and Harvell, 1999; Gilbert, 2001; Pigliucci, 2001; Lummaa, 2003; Sultan, 2003; and references therein). Phenotypic plasticity is "the rule rather than the exception" (Gilbert and Bolker, 2003), because genetic and environmental information interact to shape virtually all aspects of the organism's development and function. As our understanding of DNA enters its "mid-life crisis" (Angier, 2003), it is appropriate to restore the genetic material to its context: in an organism with integrative transduction systems that construct the phenotype. With this recognition comes an altered understanding of the genotype as coding for a set of phenotypic potentialities rather than a single, specific outcome. (Cases in which phenotypic expression is insensitive to either genetic or environmental variation are known as "canalization" [see previous chapter by Gibson]; here the phenotypic outcomes are narrowly constrained). To understand phenotypic diversity and its evolution, it helps to see organisms as systems of genotype–environment integration rather than to focus solely on DNA sequences or phenotypic trait states. In addition, to understand natural selection, it is logical to focus on the key phenotypic product of genotype–environment interaction—fitness—in the natural environment.

Although phenotypic plasticity is the general case, it is tricky to study empirically, and it is currently described by an imprecise and often inconsistent terminology. In this chapter we begin with definitions and distinctions that identify ways to conceive of the environment and of plasticity. We then discuss these issues: (1) What causes plasticity? What types of genetic architecture and signal transduction mechanisms underpin plastic responses to environment? (2) What is the nature of genetic variation for these responses? (3) How do plastic responses, expressed within a single generation, interact with the slowly changing developmental frameworks characteristic of entire clades? (4) What are the consequences of plasticity for populations and communities? We have aimed to write a constructive guide to key issues of phenotypic variation, rather than a comprehensive review of a vast field. We also hope that this chapter can serve as a research agenda for this rapidly unfolding area.

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I. PLASTICITY CONCEPTS

The concept of phenotypic plasticity encompasses many phenomena usefully subdivided by distinctions to which every researcher should be sensitive. Plasticity refers broadly to all aspects of the phenotype in which expression varies as a result of variation in the environment. This concept includes virtually all traits—morphological, behavioral, physiological, reproductive, epidemiological—and virtually all environmental factors, biotic and abiotic. The organism's expressed phenotype itself can shape its biotic and abiotic environment, creating an iterative, dynamic feedback (Lewontin, 2001; Gray, 1992). To understand the plastic response, we also need to consider the physical and biochemical state of the organism at the cell, tissue, and whole-body levels, including hormonal integration, cell–cell interactions, and the mechanisms underpinning dynamic coadaptive adjustment among traits. Thus plastic responses to the environment depend on the state of the organism, itself the product of prior genotype and environment interactions. Importantly, the internal environment often reflects events in the previous generation as well as earlier in the life of the organism.

A. Specific Types of Plasticity

One can, and some have, distinguished subsets of phenotypic plasticity based on ecological categories (e.g., plasticity for shade responses in plants), on qualitative trait categories (life-history plasticity, physiological plasticity), or on the timescale, specific mechanism, or occurrence pattern of plastic responses (Slobodkin, 1968; Piersma and Drent, 2003). Such distinctions can help to point to shared mechanisms or interpretations and are best drawn in the context of specific research questions rather than *a priori*. For instance, one might choose to distinguish irreversible developmental plasticity from rapid metabolic or physiological responses that occur on a shorter timescale, but the precise boundaries will necessarily be system specific. A case in point is that of animal behavior. Some see behavior as continuous with plasticity and doubt the utility of distinguishing between the two. They might regard behavior as a particular type of plasticity consisting of iterated, dynamic reaction norms for short-term responses, mediated by a central nervous system. Acclimation, a term from physiological ecology, is another aspect of environmental response that one could include within a broad concept of plasticity. Others prefer to limit the concept of plasticity to unique, irreversible developmental events in the lifetime of an individual occurring on a timescale that is an appreciable fraction of that lifetime.

We think it wise not to make a decision on this issue until one is confronted with a particular problem in need of solution. The problems should shape the categories used, categories judged for their utility in helping to solve the problem. The categories should not shape the problems. In some cases, for example,

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distinguishing plasticity from behavior may help. In others, viewing them as elements of a continuum may help. Rather than waste time on arguing about whether it is a good idea to adopt this distinction, we prefer to remain aware that it is a possible distinction and to reserve judgment on its utility until confronted with a concrete research problem. When we have more experience on this issue, it may be possible to recommend classes of problems in which one or the other stance is more productive. However, that is not yet the case.

B. Reaction Norms

Phenotypic plasticity can be studied by means of several types of phenotypic response data or "norms of reaction." Here we build up an array of plasticity concepts starting with the most elemental, the "genotypic reaction norm" (Woltereck, 1909; Schmalhausen, 1949; examples in Sultan and Bazzaz, 1993), then passing through a series of classes of reaction norms that integrate increasingly complex effects, and ending with a comment on the relationship of reaction norms to behavior.

The reaction norm is most precisely conceptualized as *the phenotypic expression of a given genotype for a single trait at several specified levels of a particular environmental factor*, for example, the reaction norm of a particular clone of *Daphnia pulex* for head spine length as a function of a defined range of ambient temperatures. As with all reaction norms, both the trait of interest and the environmental variable must be precisely defined, so that comparable measurements can be made on the different phenotypes produced by genetic replicates in different experimental environments. For instance, because developmental rates often vary with environment, traits may be defined with respect to either absolute age or specified ontogenetic stages (Gedroc *et al.*, 1996). In the preceding example, head spine would be measured in *Daphnia* individuals at a particular instar at each temperature. Environmental factors should be carefully controlled so as to avoid covarying changes that can confound interpretation.

From this concept we can build up to several others that are experimentally useful, particularly in organisms for which genotypic replicates cannot be readily obtained. If the study organism has many offspring, we can estimate "family mean reaction norms" by measuring several sibling offspring at each environmental level (Gebhardt and Stearns, 1992). Such family mean data provide the best estimate of reaction norms for organisms that cannot be cloned and are particularly robust when siblings are inbred full sibs (e.g., Gupta and Lewontin, 1992).

When familial relationship cannot be determined in the sample, one may still wish to compare the plastic reactions of two populations based on a random sample of individuals from each population split into subgroups and measured at a series of environmental levels. Such data represent "undefined population mean reaction norms." It is also possible to build up population mean reaction norms

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from a collection of genotypic reaction norms, then termed "genotype-based population mean reaction norms," or from a collection of family mean reaction norms, then termed "family-based population mean reaction norms."

Such distinctions, though cumbersome, are critical, because the essential aim of reaction norm analysis is to establish clarity about the genotype–phenotype relationship. Another approach taken in the literature is to reserve the term *reaction norm* for genotypic data and refer to "plasticity patterns" when the sample is genetically undefined. Whatever approach is taken, it is essential to make clear the type of data being presented.

C. Parental Effect Reaction Norms (Cross-Generational Plasticity)

"Parental effect reaction norms" refer to effects of environmental variation on the parental generation as measured in the offspring. In many systems, including flowering plants and mammals, these cross-generational effects reflect the fact that the maternal body constitutes the offspring's early developmental environment. However, this type of plasticity may also arise from environmental effects on the maternal or paternal individuals or (in self-fertilizing organisms) on both simultaneously. In estimating "family mean" parental effect reaction norms in outcrossing organisms, maternal and paternal effects can be separately estimated with a full-sib/half-sib mating design, in which case the resulting data form a sheaf of surfaces in two dimensions. With the reaction norm measured over two generations, the offspring can be measured in a single environment, or alternatively at each level of environmental factor used to define the reaction norm in the parents, thus estimating a reaction surface. The evolutionary implications of these patterns depend on offspring dispersal and the consequent distribution of environmental states across as well as within generations, information that is rarely collected. "Grandparental effect reaction norms" are known in some systems (Reznick, 1981; Wulff, 1986); their importance depends on the relationship of the generation time of the study organism to the rate of environmental change. If the effect of the environment encountered by the grandparent on the grandchild depends on the environment encountered by the parent, as is probably the case, then one needs a design complicated and powerful enough to measure the grandparent–parent interaction effects.

D. Imprinted Reaction Norms

Many organisms have a sensitive period early in life during which basic patterns are determined irreversibly for critical traits. These early environmental effects on development condition the organism's physiological and behavioral responses to

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subsequent environmental inputs. For instance, the fetal nutritional environment in humans determines not just birth weight but the state of the circulatory and endocrine systems, affecting the individual's metabolic response to subsequent nutritional states (Barker, 1998; Lummaa, 2003). Thus the interaction of environmental events at different points in the life cycle may be an important aspect of plasticity and a key step toward understanding the real-life complexity of developmental trajectories. To study these effects, one could expose organisms to a series of levels of environmental factors for a defined period early in life and then measure their reactions to those environmental factors later in life. As with maternal-effect reaction norms, such measurements will result in a sheaf of surfaces defined by three axes: level of environmental factor (1) early in life, (2) during the rearing period, and (3) later in life. We call such responses "imprinted reaction norms." Depending on the genetic structure of the experiment, they may be elemental, family mean, or undefined population mean reaction norms. Examples include birth weight of a particular population of mosquitofish as a function of the salinity of the environment in the first week of the life of the mother (Stearns, 1980) and insulin resistance, hypertension, cardiovascular disease, and obesity late in life as a function of fetal nutrition in humans (Barker, 1998; Lummaa, 2003) and rats (Vickers *et al.*, 2000).

E. Iterated Reaction Norms

Reaction norms typically describe environmental reactions for a single trait that is expressed once in the life of an individual or that can be measured at a single meaningful point. However, some traits, such as clutch size in iteroparous organisms, are expressed repeatedly. Their repeated expression raises the possibility that the second expression depends on the first, as is known to be the case with clutch size in many birds--a type of cumulative parental effect. The third expression could in principle depend on both the first and on the second expression, and so forth. Reactions that depend on events occurring repeatedly in the life of the same organism are termed "iterated parental-effect reaction norms."

The gentle reader may wish to consider the insights that might be gained by attempting to measure the multidimensional objects carrying the label of "family mean, parental effect, imprinted, iterated reaction norms." The difficulty of measuring them detracts neither from the logic that indicates the plausibility of their existence nor from their importance as complicated elements of the genotype–phenotype map. It is interesting to contemplate how far out into the web of causation suggested by that label adaptation and identifiable genetic and environmental effects could be tested and applied. In addition, it is worth noting that simply uttering the label suggests the kinds of experimental controls needed to isolate particular effects.

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F. Dynamic Reaction Norms

In some cases, reaction norms may be of interest for inherently dynamic traits, such as growth rates, or for traits that comprise continuous responses to temporally variable environments. Indeed, in indeterminately growing organisms such as plants and some animals, development itself is such a trait, and the norm of reaction must be conceived as a dynamically and continuously remodeled phenotype. This concept describes the continuous readjustment of root morphology as growing roots encounter different soil environments, the continuous replacement of surface proteins in the malaria pathogen, and the continuous updating of the status of the vertebrate immune system as organisms encounter, respond to, and "remember" pathogens.

II. THE GENETIC AND DEVELOPMENTAL BASIS OF PHENOTYPIC PLASTICITY

To understand phenotypic plasticity as variation subject to evolutionary change, we must trace the complex causal chains that link ecologically meaningful patterns of plastic response to underlying developmental pathways through specific genetic and environmental components. This is of course a demanding research program and one that is likely to require collaborative efforts across biological disciplines (Callahan *et al.*, 1997). Our success will depend both on careful studies of genetic cascades and signal transduction pathways and on a developmental paradigm that accommodates the real-world complexity of phenotypic expression (Gilbert, 2001). To some extent, the study of evolutionary development provides a model for comparisons of regulatory cascades and their genetic components. However, thus far this kind of "evo-devo" study has focused on the few highly conserved genes involved in major structural traits such as generation of body axes and location of appendages and sense organs (Carroll *et al.*, 2001; Wagner, 2000). The mechanisms of subtler aspects of development such as plasticity involve more transient, interacting regulatory events that incorporate the whole dynamic apparatus of environmental signal transduction (Carroll *et al.*, 2001).

At present, the precise developmental pathways underlying patterns of phenotypic plasticity are known in only a few cases (Pigliucci and Schmitt, 1999; Schlichting and Smith, 2002; Nijhout, 2003). Here we review two of the best-documented: morphogenetic response to shade in green plants and plasticity for metamorphic rate in amphibians (a third elegant example, butterfly wing spots, is discussed in a later section). These cases are particularly compelling because the adaptive consequences of the response are well understood. In choosing these two examples, we emphasize a common paradigm for studies of plasticity in diverse organisms. In our view, shaping such a general paradigm (and a correspondingly

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inclusive terminology) is an important step toward incorporating plasticity into both evolutionary and developmental biology. As mentioned previously, this is one reason for avoiding categorical distinctions in types of plasticity that are unlikely to apply well to all organisms (Schlichting and Smith, 2002).

Rather than add to parallel literatures on plant and animal plasticity that are necessarily both redundant and incongruent, one can specify within a general framework how developmental differences between these groups are likely to affect their expression of plasticity. For instance, animals have highly differentiated cells in relatively rigid developmental trajectories. In "higher" (bilaterian) animals, few tissues are expected to retain plasticity in adulthood, and the body plan is ordinarily fixed (Walbot, 1996). In contrast, plants express plasticity continually at both the cell and organ levels and continue to form and extend body parts throughout life. Indeed, the fate of differentiated cells in the adult plant body can change, for instance, in response to a wound (Walbot, 1996). In addition, each meristem on a plant body is capable of independent response to environmental signals, because there is no single central tissue analogous to the nervous system (Gilroy and Trewavas, 2001).

These differences lead to three distinct predictions: First, in contrast with plants, the kinds of plasticity expressed by animals will change during the life cycle (e.g., from developmental to physiological and behavioral). Second, plastic responses in animals may be more highly integrated at the whole-organism level because of joint nervous and endocrine control. Third, many structural traits will be highly canalized in animals but not in plants. Colonial organisms, fungi, and microorganisms will also have particular modes of plastic response that reflect both cellular constraints and emergent developmental repertoires, for instance, in lichens and biofilms. Recognizing these kinds of differences among organisms can inform our research questions and lead to a more sophisticated understanding of the nature of plasticity in general.

A. Photomorphogenetic Plasticity in Plants

Plants perceive impending shade by neighbors as a change in light spectral quality (Ballaré *et al.*, 1987). Perception of these spectral signals initiates "shade avoidance" responses such as internode elongation and suppressed branching (Casal and Smith, 1989) that have been shown to enhance fitness in dense plant stands (Schmitt *et al.*, 1995; Dudley and Schmitt, 1996). In contrast to other aspects of the plant environment, the perception mechanism for these adaptive plastic responses is both well understood and straightforward (Schmitt *et al.*, 1999; Gilroy and Trewavas, 2001). Most plants perceive and transduce this subtle cue with phytochrome photoreceptor molecules (Smith, 1995), which are sensitive detectors of small changes in the red to far-red (R to FR) ratio of incident light. Such changes

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directly modify the ratio of two photoconvertible forms of the phytochrome molecule (Pfr to P) in vegetative tissues. The morphogenetic impact of this chemical signal is remarkably rapid: Low Pfr/P in a growing stem induces growth promotion with a lag time of only 10 minutes and a reversal lag of 16 minutes. The magnitude of the stem elongation response depends on how low the R to FR light ratio is and for how long, as well as when in the diurnal photoperiod the low ratio occurs (Casal and Smith, 1989).

Specific loci that encode several phytochrome proteins have been sequenced in *Arabidopsis thaliana*, and photoreceptor-deficient mutants have been isolated that show disabled plastic responses to light (Callahan *et al.*, 1999; Pigliucci and Schmitt 1999). Studies of these mutants and of transgenic constructs have demonstrated the distinct though partly overlapping light-sensing and regulatory functions of these phytochrome genes, which constitute a "gene family" with both evolutionarily conserved and more rapidly evolving, variable functional domains (Schlichting and Smith, 2002). The phytochrome genes interact throughout development to regulate a host of ecologically important morphological and life-history traits (Schmitt *et al.*, 1999, and references therein). Similarly, two *Arabidopsis* blue light receptors encoded by paralogous genes initiate signaling pathways that are partly redundant, but because of differential sensitivities, act to cue phototropic response in different light habitats (Galen *et al.*, 2003). Gene duplication and regulatory diversification can thus enable the origin of novel plastic responses that, if adaptive, can be reinforced by natural selection. These fascinating studies show how genetic variation at the molecular level contributes to the epigenetic regulation of adaptive phenotypic response to environmental variability.

B. Adaptive Plasticity for Timing of Amphibian Metamorphosis

Many amphibians breed in temporary ponds and face the challenge of completing metamorphosis to the terrestrial form before their aquatic larval environment dries up. Because the rate of pond drying is unpredictably variable, plasticity for rate of development provides an adaptive solution to the fitness trade-off between risk of larval mortality and maximal size at metamorphosis (Newman, 1992). Several species, particularly those living in dry habitats, are able to accelerate metamorphosis in response to the onset of pond desiccation. Such species can show a continuous, graded acceleration in developmental rate that correlates to the rate of water loss in drying ponds (Denver 1997a,b, 1998; Denver *et al.*, 1998; Boorse and Denver, 2004).

How do individual animals recognize reduced pond volume, and how do they subsequently change their metamorphic rate? In the spadefoot toad *Spea hammondii*, a carefully controlled study eliminated several potential covariates of pond drying

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as cues for the plastic response: water temperature, chemical concentration, and physical interactions among more crowded tadpoles. Instead, the tadpoles sensed their imminent risk by perceiving both a reduction in swimming volume signaled by their own reduced movement and closer proximity to the water surface perceived either visually or through changes in water pressure (Denver *et al.*, 1998). These environmental signals initiate an increase in corticotropin-releasing hormone (CRH) in the brain, which in turn rapidly activates two distinct endocrine systems that control metamorphosis, the thyroid and the interrenal (Denver, 1997a, 1998). Thyroid hormone and other hormones released by these systems regulate gene expression to shape the suite of morphogenetic changes that comprise metamorphosis, from limb development to dramatic remodeling of the gut (Shi, 1994).

Since CRH is considered the primary stress neurohormone in vertebrates, its role as a mediator of complex environmental signals may be phylogenetically linked to various types of developmental plasticity, including for instance early parturition in mammals resulting from fetal stress (Denver, 1997b). Despite such profound evolutionary conservation, congeneric amphibian species can evolve to use different environmental cues to initiate accelerated metamorphosis, because diverse sensory cues may be transduced through the neuroendocrine system to elicit similar hormonal events (Denver, 1997a). Subtle changes in sensitivity to various environmental signals, shaped by selection depending on cue reliability and perception, would act upstream of CRH to create diverse cues for a similar adaptive plastic response. In another spadefoot toad, *Scaphiopus couchii*, the increased density of tadpoles in a drying pond functions as the metamorphic stimulus, probably through increased physical interactions among the more crowded individuals (Newman, 1994). In *Scaphiopus multiplicatus*, the environmental signal is directly hormonal: As pond volume declines, the density of brine shrimp increases, and tadpoles ingest more of these prey items with their high constituent levels of thyroid hormone (Pfennig, 1992). Although the molecular variation that underlies these cases remains to be fully understood, these studies demonstrate the interplay of conserved and variable transduction events that enable plastic responses to environmental challenges.

C. Mediation of Phenotypic Expression

Let us now summarize the picture of the developmental process that emerges from these and a host of molecular developmental studies (see also discussions by Nijhout, 1990, 2003; Stern, 2000; Stearns, 2003; Sultan, 2003). Development integrates both genetic and environmental information through a complex series of regulatory steps. External environmental signals are transduced into internal signals by the organism in specific ways that depend on its sensory and metabolic

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systems, typically by means of hormones and other signals. (In some cases, environmental conditions can directly affect the action of transcription factors, as in the case of heat shock proteins.) The effects of a given hormone or other signal vary depending on the type of cell, tissue, or organ as well as on developmental stage and on other environmental conditions (Voesenek and Blom, 1996; Gilroy and Trewavas, 2001); cells can differ in the threshold at which they initiate a response as well as in the response duration and magnitude (Gilroy and Trewavas, 2001). That response is accomplished in many cases by the cell signal (either directly or through a secondary messenger or "transducer") binding to nuclear DNA. (Some plastic responses may also result from phosphorylation and protein activation cascades rather than novel gene expression, something we suspect in principle without yet knowing in fact; H. F. Nijhout, personal communication, 2004.) This event elicits a regulatory cascade that consists of the expression of transcription factors that bind to the control sites of many genes, inducing expression patterns that upregulate or downregulate networks of subsequent gene activity with phenotypic consequences. These transcription factors can be either "promiscuous" or targeted in the genomic regions they affect, and their effects on gene expression can be cell-specific, tissue-specific, and stage-specific (Carroll *et al.*, 2001). The effects of mediating cell signals on gene expression are thus both phenotypically specific and highly pleiotropic (Ketterson and Nolan, 1999). Furthermore, many developmental processes are conditioned by multiple rather than single hormonal signals. Clearly, the regulatory systems that integrate these many internal and external signals involve substantial interaction and "cross-talk."

In sum, then, phenotypic expression is mediated by a layered network of regulatory events, from environmental signal transduction to coordinated effects on gene expression with specific morphogenetic and physiological results. One critical implication of our increasingly sophisticated understanding of developmental mechanisms is that the underlying pathways of plastic response are no different in nature from those of other developmental processes (see Schlichting and Smith, 2002). Plasticity may differ in the range of possible phenotypic outcomes for a given trait and organism, but not in the nature of its genetic mechanisms. As developmental genetics has matured, its initial goal of identifying genes with pronounced effects on certain developmental events has shifted to the goal of understanding gene regulation—that is, the complex interplay of signal transduction, epigenetic interactions, and physical and biochemical factors that regulates gene expression and consequently underlies the process of development (Carroll *et al.*, 2001). Because development in general depends on regulatory cascades that include signals from both external and internal environments, there is no reason to posit that phenotypic plasticity requires a distinct genetic architecture or regulatory process. Indeed, it has become increasingly clear that plasticity per se is not regulated by genes separate (and separately evolving) from those that otherwise affect traits (Scheiner and Lyman, 1991; Kliebenstein and Mitchell-Olds, 2002).

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Several studies have concluded that plastic responses even to such a relatively straightforward environmental factor as temperature point to a complex epistatic system of gene regulation (Scheiner, 2002). Published data have not readily distinguished alternative hypotheses about underlying genetic architecture (Scheiner and Lyman, 1991; Karan *et al.*, 2000; see also Wu, 1998). In general, the lack of simple correspondence between genotypic and phenotypic variation (Stern, 2000) suggests complex regulatory systems. Even the quantitative trait locus (QTL) approach, which identifies entire regions involved in multilocus traits, may not encompass the genetic complexity of these systems, for this approach cannot resolve many small regulatory effects (Vitzhum, 2003), and different QTL alleles may be expressed in different multifactorial environments such as growth season (Weinig *et al.*, 2002).

Those cases of phenotypic expression that we characterize as "plastic" may simply entail a relatively broad diversity of outcomes, compared with "canalized" regulatory systems, in which environmental effects are buffered such that phenotypes are more uniform (see previous chapter). According to Nijhout (2003), the inevitable and likely maladaptive sensitivity of individual development to environmental factors such as temperature and ionic concentration that directly affect chemical and metabolic processes has been shaped by evolution of regulatory pathways in one of two directions: either to refine this environmental sensitivity into adaptive norms of reaction (i.e., plasticity) or to buffer it through developmental canalization and physiological homeostasis (similar to developmental buffering of genetic variation). Thus canalization and plasticity can be understood as two sides of the same evolving developmental coin; rather than define them both as special kinds of gene regulation, both can be seen *as* gene regulation (Stearns, 2003). Note that what may appear to the researcher as distinct alternative phenotypes may just be those discrete points on a continuous norm of reaction that are expressed because of (natural or experimental) environmental discontinuities, not necessarily the result of some exceptional kind of major developmental switch (Stearns and Hoekstra, 2000; Karan *et al.*, 2000; Nijhout, 2003). At this point, few studies have included enough environments to assess an entire norm of reaction (Karan *et al.*, 2000; see Windig, 1994, for a well-analyzed case), so these distinctions have perhaps been overly emphasized.

Recent theoretical results on networks of gene expression also call into question the idea that canalization—and, by inference, plasticity—is a distinct developmental phenomenon demanding special explanation. Model genetic regulatory networks that are allowed to evolve to maintain function despite knock-out mutations in randomly chosen genes have, as a by-product, the buffering of the expression of the genes in the network (Siegal and Bergman, 2002). Knock-out mutations in yeast appear to occur in a real-world context that has similar properties (Bergman and Siegal, 2003). After Waddington (1960) suggested that canalizing mechanisms evolved to buffer phenotypes against genetic and environmental

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perturbations, canalization came to be seen as a real phenomenon caused by distinct genes and regulatory mechanisms. However, the property of canalization may simply be a by-product, and not necessarily a well-localized by-product but a diffuse property of the entire control network rather than any single gene. The same insight may well apply to plasticity.

The fact that plasticity does not call for a distinct developmental genetic paradigm does not at all lessen the importance of plastic expression as an aspect of phenotypic variation, but it does suggest some changes to our research questions. It remains fundamentally important to evaluate the ecological and selective consequences of environmentally contingent patterns of phenotypic expression versus buffered, canalized expression, but we believe our understanding of the underlying mechanisms and their evolution should be integrated into broader investigations. For instance, possible "costs of plasticity" should be studied in the general context of gene regulation, rather than assumed to be inevitable results of a uniquely cumbersome genetic architecture. If plasticity does depend on the same kind of regulatory pathways as do more uniform phenotypic outcomes, this would account for the fact that despite considerable effort the evidence for the costs of plasticity is scant at best (Dorn *et al.*, 2000). Constraints on the evolution of plasticity may reside more in phylogenetic or environmental limits to accurate cue perception and transduction than in hypothetical costs (Sultan and Spencer, 2002). Most importantly, this insight changes our approach to development in general to one in which both environmental context and genetic constituents interact in a dynamic integrative process (Lewontin, 2001; Sultan, 2003).

D. Genetic Variation and the Evolution of Plasticity

One challenge is to incorporate this view of development as both dynamically complex and context dependent into our notion of heredity. It has become clear that a linear model of causation running from gene to phenotype is rarely true, that the phenotype emerges from an epigenetic system that integrates interacting genes and gene products with both internal and external signals (Trewavas and Malho, 1997). Increasing knowledge of molecular mechanisms, combined with advances in evolutionary development, have made clear that it is these complex epigenetic systems that "descend with modification," not specific genetic variants or alleles. Starting with Waddington (1960), several artificial selection experiments have shown clearly that norms of reaction are heritable and can evolve (Hillesheim and Stearns, 1991; Scheiner and Lyman, 1991; Brakefield, 2003, and references in these papers; see Scheiner, 2002, for full discussion). Indeed, artificial selection can shape plasticity patterns (the slope of reaction norms to post-hoc response-ordered environments) in as few as five generations (Falconer, 1990; Hillesheim and Stearns, 1991). However, there have been relatively few studies of selection

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directly for plasticity (Fischer *et al.*, 2000); more often artificial selection on other traits has produced correlated effects on plasticity patterns (Scheiner, 2002).

One important goal of these selection experiments has been to clarify the genetic architecture of plastic response, which will of course affect evolutionary predictions (Via *et al.*, 1995). Unfortunately in this area "theory has far outstripped data" (Scheiner, 2002). The complex genetic basis of these response systems—and the view that plasticity is a difference in outcome and not mechanism—is confirmed by findings that selective change in the mean and plasticity of a trait are interrelated (Scheiner and Lyman, 1991; Kliebenstein and Mitchell-Olds, 2002). Although there is clearly widespread genetic variation for reaction norms in natural populations (revealed in quantitative genetic studies as significant genotype by environment interaction or "$g \times e$"; Falconer and Mackay, 1996), the molecular basis of this variation is still largely unknown (Scheiner, 1993; Wu, 1998; Nager *et al.*, 2000; Kliebenstein *et al.*, 2002; Nijhout, 2003). This is in part because of the complexity both of the phenotypic traits studied and of the environmental factors that elicit variation in those traits (Kliebenstein *et al.*, 2002). One approach is to use QTL to map major loci that influence differential gene expression in different environments (Jansen *et al.*, 1995). For instance, Lukens and Doebley (1999) identified a difference at a single QTL locus between maize and its wild ancestor teosinte that contributes to reduced architectural plasticity in response to density, evidently through a change in regulation rather than in protein coding. The QTL approach will no doubt remain very useful, despite its limited resolution. However, in cases where $g \times e$ interaction is influenced by many genes of small effect, it may be impossible to resolve in mapping experiments (Stratton, 1998; Vitzthum, 2003).

Like other aspects of phenotypic variation, potential for norm of reaction evolution will vary among traits and taxa depending on available genetic variation and on phylogenetic, developmental, and other constraints. Consequently, even direct selection for plasticity may produce no response (van Kleunen *et al.*, 2002). Artificial selection for high versus low plasticity for temperature-induced adaptive variation in butterfly wing patterns revealed genetic constraints to change in plasticity, possibly because of positive genetic correlations across temperatures (Wijngaarden and Brakefield, 2001). Fischer *et al.* (2000) artificially selected for change in the spatial plasticity of clonal spread in buttercups, an important aspect of competitive response in the field. Despite substantial genetic variation for the trait ($g \times e$ interaction), no response was found after two generations of selection, suggesting that additive genetic variation contributing to plasticity may have been depleted in these natural populations because of previous selection. Like other adaptive traits, plasticity for ecologically important responses may thus show relatively low response to selection (Scheiner, 1993; Fischer *et al.*, 2000). One interesting aspect of evolutionary constraint is specific to plasticity: When some traits are plastic, genetic correlations among traits and therefore response to selection

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will vary from one environment to another (Newman, 1988; Hillesheim and Stearns, 1991).

Evolutionary change in plastic response—and phylogenetic constraint to such change—can occur at any link in the intricate causal chain that regulates phenotypic expression, from the initial perception of an environmental cue, to its transduction as an internal (often hormonal) signal, to cellular reception mechanisms, to transcription factors, to sequence variation in DNA-binding sites, to gene expression. Clearly many points of regulation can evolve (Nijhout, 2003); "genes for plasticity" can refer to heritable change at any of these levels. Indeed, cryptic variation within and among populations can occur from variation at any of a number of points in the regulatory cascade (A. C. Burke, personal communication, 2004). Mutational changes to upstream receptors may alter many aspects of gene regulation and thus have broad pleiotropic effects, while allelic changes to the promotor regions of downstream genes are likely to show more specific effects on the phenotype (Stern, 2000; Kliebensbeck *et al.*, 2002, and references). For instance, a QTL "for" plasticity might be a region of a chromosome that codes for a transcription factor. In a carefully focused study on the production of a plant defense compound with a known genetic basis and hormonal signal, Kliebenstein and Mitchell-Olds (2002) showed that the same QTL regulated both the plasticity of defense biosynthesis and its mean level. Interestingly, they found substantial among-population variation in the signal transduction pathway even for this biosynthetically simple secondary metabolite. Genetic variation for regulatory proteins is probably a key aspect of variation for plasticity. Conversely, similar plastic response patterns may result from different evolutionary changes in the underlying regulatory cascade. At a higher level in the regulatory chain, genetic changes in hormone physiology can affect many seemingly unrelated developmental traits (Voesenek and Blom, 1996). At its end, changes to the sensory and behavioral apparatus for environmental perception will alter the initial steps in signal transduction that initiate the entire cascade. Future research on the evolution of plasticity must be aimed at understanding both genetic variation at these diverse points in the process and the evolutionarily conserved aspects of environmental perception, hormonal control, transcription, and expression that constrain the evolution of plastic responses systems (deWitt *et al.*, 1998; Ketterson and van Nolan, 1999).

III. HOW PLASTICITY INTERACTS WITH CONSERVED DEVELOPMENTAL PATTERNS

One of the major biological discoveries of the last 20 years is the existence of deeply conserved developmental patterns controlled by equally conserved genes. Examples include *HOX* control of the development of the body axis of arthropods

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and vertebrates, *HOX-d* control of vertebrate limb development, and the *MADS* genes that interact in the ABC model of angiosperm flower development (Carroll *et al.*, 2001; Weigel and Meyerowitz, 1994). One possible inference is that with the exposure of these developmental mechanisms we have discovered the origin of phylogenetic constraints and the explanation of Baupläne. Whether that is the case or not, this much appears to be true: Some aspects of developmental regulation change very slowly and are nearly invariant within fairly large clades. If some developmental pathways change slowly, with rates measured in phylogenetic time on a scale of many millions of years, then how do those pathways interact with the variation in regulatory steps involved in plasticity, which occurs within a single generation?

The butterfly wing has been developed beautifully as a model system that would appear to be ideal to answer this question. It is a flat sheet of cells with many natural markers, such as wing veins and compartment boundaries. The possible locations of eyespots and stripes within that system of natural markers—the so-called Nymphalid Ground Plan—appears to be fairly invariant within a large clade of butterflies (Nijhout, 1991). The development of the butterfly wing can be manipulated through surgery on wing discs that lie on the surface of metamorphosing pupae. For example, eyespot primordia can be transplanted to new locations, producing eyespots where none occur in nature (Brakefield *et al.*, 1996). The genetic control over the development of some of its major features, including eyespots, is now quite well understood and has been shown to involve developmental control genes with known functions in *Drosophila* and other insects. For example, *distal-less* is expressed at the distal tips of *Drosophila* appendages and plays a role in determining whether the appendage turns into an antenna or a leg, and if a leg, which leg. It thus provides positional information; its expression signals to the surrounding cells that they are at the distal end of an appendage. In the butterfly wing, this is the gene whose expression triggers the development of eyespots, which are in the middle of the wing blad—not anywhere near its distal end—a good example of cooption of an existing developmental regulatory mechanism to a new function (Brakefield *et al.*, 1996).

These eyespots undergo adaptive seasonal change, a form of plasticity known as seasonal polyphenism (Shapiro, 1976). In the best-studied case, *Bicyclus anynana*, a tropical African butterfly, the selective reasons for the seasonal change have been investigated in the field. The eyespots are large in the wet season, small in the dry season. When the dry season forms are released in the wet season, they have lower fitness than wet season controls. The selective pressure is predator avoidance—what is cryptic in the dry season is not so cryptic in the wet season. Laboratory experiments have established that the seasonal changes in the size of the eyespots are in fact not a discontinuous polyphenism but a continuous reaction norm that appears to be discontinuous in the field simply because the temperatures that induce the change in development differ between seasons. All intermediate forms

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can be reared by using a range of temperatures in the laboratory (Windig, 1994). This impressive and actively growing work can be accessed through Brakefield (2000), Brunetti *et al.* (2001), Beldade and Brakefield (2002), Beldade *et al.* (2002c), and Monteiro *et al.* (2003). It builds on insights that can be traced through Nijhout (1991), who played a key role in the development of the system, back to Schwanwitsch (1924), who first recognized the Nymphalid Ground Plan.

At first, this system appears to offer a straightforward answer to the question addressed here: How does plasticity interact with conserved developmental patterns? Plasticity would appear to be a short-term response embedded in an ancient framework. The shared ancestors of butterflies and flies had developmental control genes that shaped appendage structure. In the fly they controlled the development of legs and antennae; in the butterfly, of wing spots and stripes. The positional information was phylogenetically conserved in developmental control genes whose expression was constrained. They could only induce the production of spots and stripes in certain parts of the wing and not in others. Once, however, it had been determined that an eyespot was going to develop in a certain place, its size and color could be altered during the development of a single individual by temperature. This gives a fairly classical picture of a phylogenetically conserved, rigid developmental pattern expression early in development that laid down structures that were then subject to "fine-tuning" by plasticity later in development. The developmental control genes, in particular *distal-less*, created a vase, the eyespot, in which we could conceptually place a bundle of reaction norms for size and color like a spray of flowers representing the phenotypic plasticity of the butterfly population in seasonal Africa. Just as a vase holds a bouquet of flowers on a table, so did the phylogenetically conserved developmental control over the eyespot hold the reaction norms in position on the wing.

A. Genetic Causation and the Butterfly Wing: A More Complicated Picture

We are no longer convinced that the simple metaphor of a vase with flowers is a helpful way to think about the system, because we believe this view is based on problematic assumptions about the nature of genetic causation. Our uncertainty arises from remarkable new experimental results on butterfly wings (Beldade *et al.*, 2002a,b; Monteiro *et al.*, 2003), from the new understanding of complex regulatory control on gene expression discussed in the preceding text, from the history of explanations of the segmentation of the *Drosophila* embryo, and from questions about the impact of solid geometry on the expression of developmental control genes. Bear with us while we sketch these key elements of a more complicated and indeed more interesting picture.

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First, recent experimental results make clear that the simple conserved genetic architecture of eyespot expression is in fact neither simple nor conserved.

- Artificial selection can uncouple the size of the anterior and posterior eyespots, essentially removing one while retaining the other (Beldade *et al.*, 2002b). Thus it is fairly straightforward to eliminate one eyespot module while retaining another.
- One of the genes responding to selection for eyespot size is *distal-less* itself (Beldade *et al.*, 2002a). Thus the gene thought to represent a deeply conserved phylogenetic constraint itself responds rapidly to microevolutionary selection pressures with allelic change.
- In *B. anynana* there are normally seven eyespots. X-ray mutagenesis yields mutants that remove some eyespots but not others—three and four either reduced or completely absent; one, two, three, and four absent; one, three, four, and seven absent; and all absent (Monteiro *et al.*, 2003). These results suggest that the differentiation of eyespot foci in each wing cell is controlled by one or more focus regulator genes that are under the control of regional regulator genes. Mutations to the local regulators have local effects; mutations to the regional regulators have regional effects. Some mutants yield wing patterns not found in any of the 80 existing species of *Bicyclus*, including some thought to be forbidden by the Nymphalid Ground Plan.

To summarize, not all conceivable changes in butterfly wing patterns can be selected, nor does mutagenesis produce all conceivable variants. Thus the concept of a basic butterfly wing pattern remains intact, as does the idea that an eyespot is a module. However, questions have been raised about how one should think about genetic determination: Clearly the same gene is involved in both macroevolutionary patterns and microevolutionary change. Developmental control genes are not hands-off managers that initiate development and then leave the scene; they are micromanagers that remain involved in the details of the process until it is complete (Akam, 1998). Artificial selection readily modifies eyespots separately, so each eyespot must have independent genetic control as well as general modular control. In addition, x-ray mutagenesis produces completely novel variants, including those outside the accepted possibilities of the classical model.

The second source of uncertainty is the emerging picture of transcriptional control in eukaryotes, a picture that is becoming increasingly detailed (Stern, 2000). As discussed in the previous section, eukaryotic genes are *cis*-regulated by the binding of transcription factors to upstream control regions. For example, in *Drosophila* whether or not a gene will be expressed, and the level at which it will be expressed, is determined by the binding of from 1 to 20 transcription factors to the control region. Some transcription factors bind only to the control regions of only a few genes, but many bind to those of hundreds of genes. Some may even bind to a considerable fraction of the whole genome.

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Now take that picture, and apply it to the control over the production of a module, the eyespot, in the butterfly wing. There may well be a cascade of regional and local effects, as the mutagenesis experiments suggest, but they are effects felt in a network of hundreds of genes. In addition, some of the genes thought to be triggering the cascade, such as *distal-less,* are themselves part of the fine-tuning of the module.

The third source of uncertainty is the history of explanations of segmentation in the *Drosophila* embryo, a history that addresses questions about the genotype–phenotype map rather similar, in an abstract way, to those addressed by canalization and plasticity. Turing (1952) suggested that segmentation could arise as a result of gradients of interacting morphogens producing stripes of concentration as they diffused in a cylinder. Meinhardt (1982) developed this idea into a mathematical model that appeared to produce all the essential features seen in the early segmentation of the *Drosophila* embryo. However, when the molecular mechanisms were exposed (Nüsslein-Volhard and Wieschaus, 1980; St. Johnston and Nüsslein-Volhard, 1992), we learned that stripes in embryos could be produced by entirely different mechanisms relying on local interactions of gene expression rather than global patterns of reaction-diffusion. Thus Turing's elegant insight became another "beautiful idea killed by an ugly fact," reminding us of the wisdom of agnosticism until beautiful ideas have survived rigorous tests. There are many possible alternative explanations lurking in the complexities of the genotype–phenotype map, and some of them doubtless apply to the links between phylogenetic constraints and phenotypic plasticity.

The fourth source of our uncertainty arises simply from the contemplation of three-dimensional geometry. When *distal-less* is expressed in *Drosophila*, it is near the distal tip of a narrow cylinder. When *distal-less* is expressed in *Bicyclus*, it is well within a flat, nearly two-dimensional sheet of cells. How much of what we attribute to the "control" of *distal-less* over the production of eyespots results from a targeted evolutionary modification of its activity, and how much results from more global events that restructured the appendage from a cylinder to a sheet? We cannot know without being able to make a fly turn a developing leg into the flat sheet of a wing or being able to make a butterfly turn a wing into the thin cylinder of a leg and then studying what *distal-less* elicits in the changed geometry. We might be surprised by how much results from the geometry and its consequent cell–cell interactions and not to this particular gene.

B. The Same Networks May Give Rise to Both Plasticity and Constraint

Let us now return to the original idea, the notion of a phylogenetic constraint holding a bundle of reaction norms like an old and durable vase holding an ephemeral bouquet of flowers. In some general sense that may be an appropriate analogy, but

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an unknown part of it may be a naive reification. For one thing, the components of the vase may themselves be part of the bouquet. We may thus think we see plasticity fine-tuning the phenotype within a long-established framework of phylogenetic and developmental constraint, when in fact one network of interactions may be causing the entire pattern, interactions of effects that cannot be cleanly assigned on the one hand to phylogeny and constraint and on the other hand to plasticity, interactions that produce both the appearance of constraint in one and the appearance of plasticity in another part of the same system, both as by-products. Thus we see research on the mechanisms that produce plasticity merging completely with research on the mechanisms of development in general, with the new element being systematic study of the interactions of developmental mechanisms with environmental inputs.

IV. WHAT EFFECTS DOES PLASTICITY HAVE ON POPULATIONS AND COMMUNITIES?

Although the mechanisms that cause plasticity are best approached at the level of the individual organism, many of the most important consequences of plasticity are realized at the levels of populations and communities. Population dynamics can be viewed as systematic change in the population density encountered by individual organisms, and their reactions to that change in density are a very important type of phenotypic plasticity: As population density declines, the surviving individuals each have more to eat, and they respond by growing faster to larger sizes and producing more offspring. As density increases, individual growth rates decline, fecundity drops, and mortality increases. Thus phenotypic plasticity lies at the center of density dependence. The magnitude of such effects is illustrated by the reactions of California sardines to the sharp decline in density they experienced when their population crashed in the 1950s (Murphy, 1967): near the end of the crash, only a few adult sardines were being caught, but some of them were 50-cm long and had enormous fecundities.

Ecologists have traditionally translated such responses into models that implicitly assume population mean reaction norms and ignore genetic variation in reaction norms. The loss of insight caused by making that simplifying assumption could be significant (cf. Barbault and Stearns, 1991). To see why, we build up a picture of what is going on from the reaction norm perspective. First, consider a fitness measure, b/d (b = per capita birthrate, d = per capita death rate) as a function of its own population density and that of a competitor (Figure 14-1). As its own density increases, the fitness measure declines from above 1.0 to below 1.0. As the density of its competitor increases, it does the same with different details. The population-mean reaction norm is thus a reaction surface describing the response to changes in density of both species. Species 1 replaces itself at all

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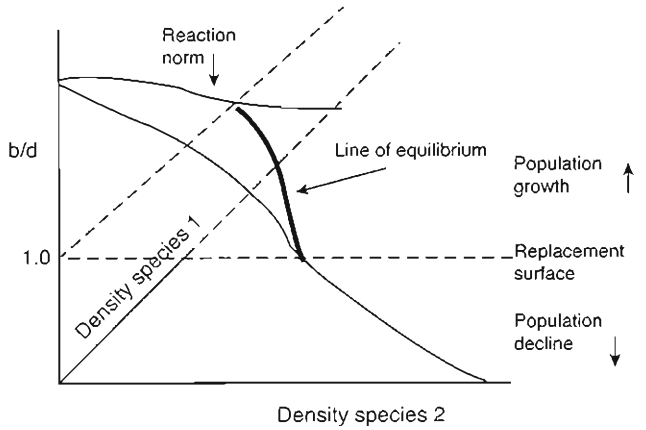

FIGURE 14-1. Density-dependent population-mean plasticity in fitness defined as b/d response to the density of one's own species (species 1) and a competitor (species 2). (Reprinted from Acta Oecologica, Vol. 12, Barbault & Stearns, "Towards an evolutionary ecology linking species," pp. 3–10, Copyright [1991], with permission from Elsevier.)

combinations of densities of its own population and that of its competitor where $b/d = 1.0$. This happens along the line of equilibrium depicted, which is nothing more than the Lotka-Volterra or Tilman zero-growth isocline (ZGI). When we add the population mean plastic response of the second species (Figure 14-2), we see that the system can have an equilibrium point at which the two species coexist. This happens when the two lines of equilibrium cross each other on the replacement surface where $b/d = 1.0$.

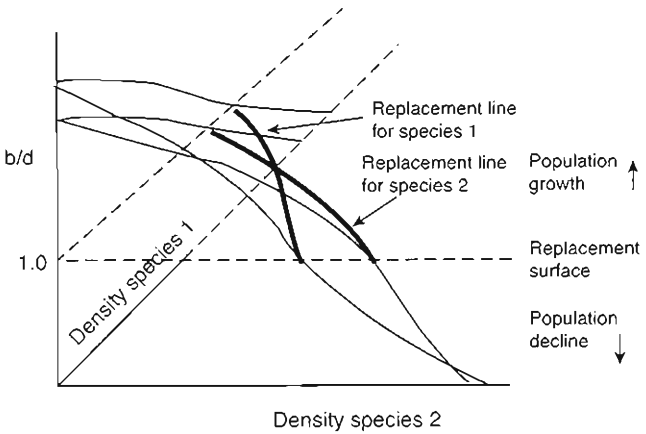

FIGURE 14-2. Density-dependent population-mean plasticity in fitness plotted for two species for the case where the species coexist where the replacement lines cross on the replacement surface. (Reprinted from Acta Oecologica, Vol. 12, Barbault & Stearns, "Towards an evolutionary ecology linking species," pp. 3–10, Copyright [1991], with permission from Elsevier.)

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Thus far we are in well-explored territory first mapped in the 1920s and revisited in detail in the 1970s and 1980s. Recently Takimoto (2003) has extended this approach, using population-mean plastic responses, to the problem of ontogenetic niche shifts. Ontogenetic niche shifts are changes in what organisms eat or where they live during their life cycle. For example, tadpoles that eat algae in ponds turn into frogs that eat insects on land. Such life cycles consist of stages with each stage interacting with a different community. Takimoto asked whether adaptive plasticity in the timing of niche shifts stabilizes consumer-resource dynamics. It would do so by accelerating the shift to the next niche if resources are scarce or delaying that shift if resources are abundant in the first niche. That plasticity will cause scarce resources to increase and abundant resources to decrease in the first niche, stabilizing the interaction, by comparison with nonplastic shifts. Takimoto's theoretical comparison of the plastic strategy with two nonplastic alternatives (shift at fixed size or fixed age) confirmed the logic of the idea: Only the plastic strategy had a locally stable equilibrium, and that equilibrium was the result of density-dependent negative feedback in resource dynamics, as postulated. The analysis was elegant, but it did not include the next step—considering genetic variation for the plastic response.

When we take that variation into account, we must put into the picture the fact that each population is a bundle of reaction norms (Figure 14-3). These reaction norms intersect the replacement surface not along a line of equilibrium, but within a certain area. That area defines the set of densities of both species within which some genotype is at its replacement density with $b/d = 1$. This is true for both species. Thus there is an area on the replacement surface defined by the intersection of the replacement sets of both species. Within that area some genotype in each species is at density equilibrium.

Figure 14-3 is a static description of a dynamic system. When we consider the dynamics, several questions arise, including these:

- Does the ecological interaction itself maintain a certain level of genetic variation? The answer will depend on whether the reaction surfaces of the genotypes of both species cross or do not cross over the ranges of densities encountered, not just on the equilibrium surface but within the volume of fluctuations about that surface.
- If reaction norms cross and recross in the space defined by the normal fluctuation of a population in response to changes in all of its biotic and abiotic interactions, then the fitness of any given genotype is always shifting up and down, and the fitness of many genotypes is varying from positive to negative. Genotype × environment interactions—crossing reaction norms—can make selection diffuse, slowing the rate of response even to directional selection (see Mitchell-Olds and Rutledge, 1986; Barton and Turelli, 1989; Gillespie and Turelli, 1989; further discussion and references in Sultan, 1987, 2003).

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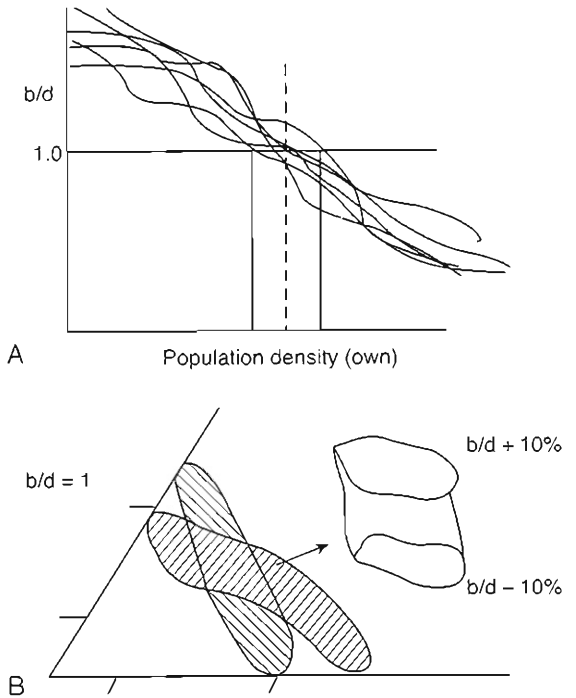

FIGURE 14-3. (A) Each population is a bundle of reaction norms, not a population mean reaction norm. The genotypes cross the replacement surface across a range of densities. At any point within that range, indicated by the dashed line, various genotypes are increasing, decreasing, or replacing themselves. (B) Replacement surfaces for both species; they replace themselves not along zero-growth isoclines (ZGIs) but within areas defined by genetic variation in their reaction norms. Both populations fluctuate above and below the replacement line in response to forces, such as resource dynamics and variation in abiotic factors, not depicted here. The volume depicted indicates where the system might be found if those fluctuations cause increases and decreases of 10%. (Reprinted from Acta Oecologica, Vol. 12, Barbault & Stearns, "Towards an evolutionary ecology linking species," pp. 3–10, Copyright [1991], with permission from Elsevier.)

- Does the existence of genetic variation for plastic response stabilize both the population dynamics of each species and their ecological interaction? It would appear to, because each species is now interacting with the other, not at a point or along a line but within a space.
- If the answer to the previous question is "yes," then we will be led to ask, how much of the stability of the natural world results from genetic variation for plastic responses to population density or to any other important ecological factor?

Answering that question requires simultaneous consideration of the ecological and the evolutionary dynamics, because the ecological interactions cause selection to change the properties of the interacting bundles of reaction norms. The evolutionary

changes in plastic response then change the ecological interactions, and so forth. Equilibrium analysis is not appropriate for such systems: only analysis of the full temporal dynamics can tell us what will happen. The questions just listed are ripe for the application of adaptive dynamics (Dieckmann, 1997), which has precisely as its goal a full temporal analysis of the dynamic interaction of evolutionary and ecological change.

V. RESEARCH AGENDA

We seek a fresh conceptualization of the genotype–phenotype map unencumbered by the historical baggage of causal models formulated decades ago. Our reflections on recent discoveries regarding the intricacies of genetic and environmental regulation has made us question the usefulness of distinguishing the mechanisms of plasticity and canalization from the those of development in general. Yet these terms remain useful categories of phenotypic expression. The day may come when the structure of the genotype–phenotype map will be laid out in enough detail to justify a new vocabulary to describe its essential features and their consequences, but that time has not yet arrived.

In the meantime, what sorts of research will help that day arrive sooner rather than later? We offer a few opinions on this very open question, in the spirit of stimulating a discussion to help others more precisely formulate their own, perhaps quite different, points of view.

Since the ubiquity of plasticity is now well established, further descriptions of plasticity will only advance knowledge if they are done in comparative, environmental, or experimental contexts that are so well structured that they produce new insights into mechanisms and consequences. That said, in many organisms the natural history of plasticity is not yet well described. In many cases we do not yet know to which factors of natural environments organisms are responding with plasticity, nor do we have comprehensive descriptions of the diversity of patterns of reaction norms within and among populations and species. As novel environmental challenges arise in many disturbed and contaminated habitats, it is particularly critical to understand the limits of plasticity and its evolutionary potential in natural populations (Gilbert, 2000).

The potential macroevolutionary role of plasticity as a starting point for adaptive divergence remains controversial (see discussions in Weber and Depew, 2003; West-Eberhard, 2003). To what degree is plasticity important in speciation and in major transitions, such as the move from water to land? Does selection on bundles of reaction norms expressed in novel environments result in genetic assimilation of novel traits? Answering such questions will probably depend on integrating norm of reaction experiments with both phylogenetic comparisons and insights from developmental studies.

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If plasticity is a by-product of environmental interactions with genetic regulatory networks, then asking what is the cost of plasticity is really not very different from asking what is the cost of development. We suspect that we will learn more by concentrating on the mechanisms of development and how they yield specific plastic responses than by focusing on the putatively unique costs of plasticity.

One of the earliest speculations about plasticity (Wright, 1931) was that plasticity in some sense substituted for or made unnecessary genetic variation. Although that claim may have resulted from a view of selection acting on populations rather than individuals, the issue cannot simply be discarded as a red herring thrown into our path by group selection. Is plasticity only involved in fine-tuning the phenotype, or is it a central and essential part of local adaptation? Are there any generalities about the relationship between the adaptive plasticity of traits and their genetic variation and evolvability?

The twenty-first century promises to witness the resolution of many open questions about the relationship of genotype to phenotype. Among those questions, those concerning the nature of plasticity and its evolution are among the most important. The nature of plasticity is essentially the nature of development; when the connection of development to environmental signals has been properly understood, we will have understood the nature of plasticity. When the consequences of plasticity for variation in reproductive success in natural populations are better understood, we will know more about how plasticity evolves and what consequences it has for population and community ecology. The major message of this chapter is that, to achieve those goals, we may have to fully integrate development into our understanding of biological variation.

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