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EVOLUTIONARY ECOLOGY AND DEVELOPMENTAL INSTABILITY

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ABSTRACT

The past decade has seen a resurgence of interest in developmental instability, reflected in fluctuating asymmetry, as a concept in evolutionary ecology. Many investigations interpret fluctuating asymmetry in populations or subsets of populations as reflecting the existence of, or at least the potential for, natural or sexual selection. However, the biological and nonbiological factors underlying the appearance of developmental instability are not well understood. For example, the ability of heterozygosity vs genomic coadaptation to have an impact on development and cause fluctuating asymmetry is still debated, though each will have important, but different, implications for the genetic structure of populations and genetic architecture of various traits. These and other issues reviewed in this chapter must be clarified in order for the concept of developmental instability to be meaningful in evolutionary and ecological studies.

PERSPECTIVES AND OVERVIEW

Developmental stability is the situation achieved when an organism has adequately buffered itself against epigenetic perturbations, displaying its developmentally programmed phenotype. When an organism has failed to buffer such disturbances, it may display signs of developmental instability. The origin

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of the disturbances is assumed to be genetic, environmental, or the product of a genotype-environment interaction. Such assumptions about the origins of developmental instability have led to the use of the developmental instability concept in a wide range of evolutionary studies.

Recently, the validity of these assumptions has been challenged (38); indeed, the nature of the factors causing developmentally unstable phenotypes is not well understood (7, 38, 47). Therefore, this review, in addition to evaluating relevant literature, aims to define those aspects of developmental instability that require resolution.

The concept of developmental stability is usually traced to CH Waddington (81–83), and his work inspired Mather (42) to seek an understanding of genetic factors underlying stable development. In the 1950s and 1960s, *Drosophila melanogaster* was a popular model system for laboratory studies of genetic influences on development (3, 67, 68, 75, 79). More recent investigations have examined natural populations of a wide range of taxa, including invertebrates, vertebrates, and even plants. Recent studies have also relied on assumptions about the genetic underpinnings of developmental instability in phrasing questions about natural and sexual selection and in employing measures of instability for conservation biology problems. Because of the increasing popularity of developmental instability studies, we must understand its causes and what it means for evolutionary processes.

Since 1986, developmental instability has been the subject of several reviews, each with a different focus, such as its measurement and evaluation (55), its use in conservation biology (21, 30, 62), and its role in sexual selection (85). All of these applications are discussed in the proceedings of a recent conference (38) reviewed by Polak & Trivers (65a).

Palmer & Strobeck (55) provided an extremely important conceptual and methodological framework in their review of fluctuating asymmetry in development. These authors, in addition to their thorough literature evaluation, pointed out several methodological peculiarities in the study of fluctuating asymmetry, the most widely used measure of developmental instability. These peculiarities included scale effects, directional asymmetry, antisymmetry, and measurement error (see also 54). Despite these authors' strong admonitions, papers continue to appear in the literature that use largely outmoded or inappropriate measures and analyses in examining fluctuating asymmetry. The most problematic outcome of the failure to use correct experimental design occurs when an improperly designed study reveals no significant fluctuating asymmetry under conditions where it was predicted to occur. As shown in this review, an ability to discriminate among various theories for the origin of developmental instability, and the elucidation of the principles by which developmental instability occurs, depends upon properly designed empirical investigations.

DEVELOPMENTAL INSTABILITY

Because the term fluctuating asymmetry is often used interchangeably with developmental instability, fluctuating asymmetry is the focus of this review. Fluctuating asymmetry is one of three kinds of asymmetry (79), all of which concern departures from bilateral symmetry. In discussing the three, we should keep in mind that these concepts or phenomena apply to populations rather than individuals.

One departure is directional asymmetry. This occurs when the majority of the members of a population or species show a departure from symmetry that consistently favors a specific side. Examples include handedness and the lateral placement of organs such as the heart and liver in humans, muscle-size asymmetries in birds (46), and the genitalic asymmetries in insects (63). Directional asymmetry is characterized by a distribution skewed to the right or to the left.

With antisymmetry, all the members of a population show an appreciable departure from bilateral symmetry, but half display it on the left side and half on the right. Examples include claw size in male fiddler crabs and paw preference in mice. In its most extreme form, antisymmetry is associated with a bimodal, rather than a platykurtic (flat), distribution. Various authors disagree as to whether antisymmetry may sometimes be an indicator of developmental instability (20, 43, 55–57).

Fluctuating asymmetry, on the other hand, is defined as small, random departures from anticipated bilateral symmetry, such that a plot of the differences between sides generates a normal distribution. A level of fluctuating asymmetry that is elevated relative to levels found in an appropriate control group is assumed to reflect reduced developmental homeostasis.

Although fluctuating asymmetry is the most common measure used to detect and describe the magnitude of developmental instability, several other measures can be informative, depending upon the species. Morphological phenodeviance (i.e. morphological abnormalities that are not associated with a particular genotype or trait) was one of the first concepts linked to poor developmental homeostasis. The concept of phenodeviance was first advanced by Lerner (32), who studied the classic phenodeviant trait of crooked toes in chickens, but he extended the concept to include extra wing veins (15) and the Podoptera phenotype (18) in *Drosophila melanogaster*. Numerous studies have focused upon the degree of morphological variation (16, 23, 66). In vertebrates, including humans, phenodeviance is often measured in the form of minor physical anomalies (13, 25). Another means of assessing developmental instability uses fractals and can be applied not only to organisms with a bilaterally symmetrical body plan, but also to other organisms, including plants (17). Zakharov (89) suggests the need to examine a suite of features, including physiological ones, to assess developmental instability.

Studies of developmental instability increased in the mid 1950s and 1960s when researchers using *D. melanogaster* and mice began empirical investigations of the relationship between genotype and fluctuating asymmetry. These studies are widely cited as supporting the relationship between inbreeding and increased developmental instability, but, as described below, several researchers have questioned the interpretations of the genetic implications of this earlier work (38).

A major impetus for the reevaluation of earlier work is the great resurgence of interest in fluctuating asymmetry and its use in empirical studies in evolutionary and conservation biology. The central question for evolutionary biology is: What are the implications of developmental instability, usually measured as fluctuating asymmetry, for the genetic structure and evolutionary potential of populations? Following this, the central question for conservation biology is: How useful is developmental instability as an indicator of genetic or environmental stress?

POPULATION GENETIC STRUCTURE AND EVOLUTION

Developmental instability will be important for the genetic structure and evolutionary potential of populations only if two major assumptions are met. First, developmental instability and genotype must be related. This relationship may involve allelic combinations at an individual locus of distinguishable effect, relative levels of genomic heterozygosity vs homozygosity, or coadaptation of gene complexes. Second, differences in developmental instability must be associated with differences in fitness.

What Is the Genetic Basis for Developmental Stability?

The genotype may influence developmental stability in three basic ways; how to distinguish among them is currently the topic of much debate (7, 38, 47). One way is through heterozygote superiority or overdominance, another is through the disruptive influences of homozygosity for dominant or deleterious recessive genes, and the third is through coadaptation. This review discusses evidence for the relationship between each of these genotypic conditions and developmental instability. The reader should remember that the evidence in each case is associative and that the actual mechanisms underlying any of these proposed associations have never been clarified.

The idea that heterozygosity underlies the capacity for developmental buffering comes from several observations. One, mentioned above, is the appearance of phenodeviants or increased fluctuating asymmetry following inbreeding, selection, or any process that reduces genetic variation (29, 32, 79). In some cases, however, inbreeding has not increased fluctuating asymmetry (28, 86). Another observation consistent with the heterozygosity hy-

pothesis is the association of greater fluctuating asymmetry with extremes of phenotypic distributions (70, 71, 77). However, not all studies reveal this association (35). Of the studies that have sought to establish the relationship between heterozygosity and developmental instability, some are comparisons of populations or species characterized by different levels of allozyme heterozygosity, which revealed that populations with more heterozygosity showed comparatively greater developmental stability (70, 72, 80). These interpopulation studies have been criticized as only suggestive and not conclusive, because the populations being compared had markedly different histories and thus differ in other features of their genetic structure and ecology that could impact levels of developmental instability (7, 47).

Two intrapopulation studies, one in trout (31) and the other in *D. melanogaster* (5), are widely accepted as directly supporting an inverse relationship between allozyme heterozygosity and fluctuating asymmetry. However, in such cases it is usually not clear whether allozyme heterozygosity itself is important or whether the effect results from linkage between the allozyme markers and other genes (but see 90). In addition to studies of fluctuating asymmetry, analyses have sought to document increased morphological variance in heterozygous animals such as the monarch butterfly, *Danaus plexippus* (16), and the mussel *Mytilus edulis* (48). Furthermore, not all studies have found the anticipated inverse relationship between heterozygosity and fluctuating asymmetry (35), and it is possible that studies revealing no association tend not to get published.

Thoday's experiments (75) present perhaps the most compelling evidence that the increased fluctuating asymmetry observed following artificial selection or inbreeding is not a function of homozygosity. In these studies, *D. melanogaster* strains were selected for high and low bristle number. Selection gains occurring in either direction were, as expected, accompanied by increases in fluctuating asymmetry. Thoday predicted that if loss of heterozygosity were itself responsible for the increase in fluctuating asymmetry, F_1 flies from crosses between lines would be more developmentally stable and show reduced fluctuating asymmetry owing to the restoration of heterozygosity at several loci. Because this prediction turned out to be false, Thoday argued that genic balance, or coadaptation, was more relevant for developmental homeostasis, and that strong selection or inbreeding breaks up homeostatic combinations of genes, causing the observed increase in fluctuating asymmetry.

Another study now frequently cited as failing to support the contribution of homozygosity to fluctuating asymmetry was conducted by Clarke et al (11) with the honeybee, which has a haplodiploid sex-determining mechanism. They predicted that inbred females, being diploid and thus homozygous for deleterious genes, should exhibit greater fluctuating asymmetry than do males. Despite an earlier report supporting this hypothesis (6), Clarke and his asso-

ciates found no consistent difference. Their results could simply reflect the effectiveness of past selection on deleterious recessives in males, an explanation that could also apply to the observations of Keller & Passera (28), who found no increase in fluctuating asymmetry in inbred ants.

However, the outcomes of several other studies are also consistent with the idea that developmental homeostasis depends strongly upon coadaptation (referred to here as interlocus combinations or genotypes). These studies are of two types, those that examine within-species phenomena and those that look at interspecific hybrids. The most complete story is that of pesticide resistance genes in the Australian sheep blowfly *Lucilia cuprina* (reviewed in 45). Single autosomal genes induce resistance to diazinon and malathion in this species. When a resistance allele first finds itself in a nonresistant genetic background, the result is an increase in fluctuating asymmetry and a decrease in relative fitness. However, a modifier allele at another locus acts to reduce fluctuating asymmetry and restore fitness. Here we have a very strong example of the interaction between specific loci and of the influence of this interaction on developmental homeostasis.

In insects, three studies have focused on developmental instability in interspecific hybrids. Ross & Robertson (69) studied two species of fire ants of the genus *Solenopsis* from a hybrid zone in several southern US states. They compared fluctuating asymmetry in *S. richteri* and *S. invicta,* and in ants from the zone of introgression and found that hybrid ants exhibited significantly elevated fluctuating asymmetry for three of the seven characters studied.

The two other studies of interspecific hybrids were conducted in the laboratory with *Drosophila* species. First, when *D. melanogaster* and its sibling *D. simulans* were reciprocally crossed (40a), female hybrids exhibited greater fluctuating asymmetry than did males and were also characterized by a high frequency of morphological abnormalities. Second, in hybrids between *D. virilis* and its relative, *D. lummei,* Orr (53) observed developmental anomalies as well, but interpretation is confounded by the fact that the hybrids lack a microchromosome. These studies are consistent with earlier work on hybrid fish (19) in that the greater the degree of genetic differentiation between the hybridizing populations, the greater the developmental instability in their hybrids.

In summary, considerable evidence supports a genetic contribution to developmental instability. However, the nature of the genetic underpinnings remains unclear. Two within-population studies show an association between homozygosity at allozyme loci and increased fluctuating asymmetry. A number of other studies support coadaptation. These differences need to be reconciled. Furthermore, the role of single genes has not been specifically addressed, nor have the implications of finding a low but repeatable heritability for fluctuating asymmetry (34, 57, 67). The design of experiments to discriminate among

these genetic models should be of high priority for future studies. Possibly, all three models could explain developmental instability, but they may operate in different species and under different conditions.

What Is the Relationship Between Developmental Instability and Fitness?

The second assumption, that fluctuating asymmetry is related to fitness, must also be addressed. An examination of this assumption actually raises two questions: Is fluctuating asymmetry related to fitness in any predictable way? How is such a relationship explained when it is found?

Information available in the literature is still insufficient to permit us to make generalizations about either question. If fluctuating asymmetry is related to fitness, the relationship could be mediated by either natural or sexual selection, or a combination of the two. Although studies of fluctuating asymmetry and sexual selection have become popular, studies of fluctuating asymmetry and natural selection are underrepresented in the literature.

More studies have looked at the fitness consequences of developmental instability by seeking associations between asymmetries and mating success, i.e. sexual selection. The first study on the relationship between successful efforts by courting males of any species and asymmetry was conducted with *D. melanogaster* under laboratory conditions (36). In this study, wild-type males were allowed to compete, in pairs, for single females. Successful males were not only larger, but were more symmetrical for sternopleural bristle numbers, the only trait for which fluctuating asymmetry was examined in that study.

This early laboratory observation was followed by a study of natural populations of three other *Drosophila* species, *D. simulans, D. pseudoobscura,* and *D. mojavensis* (40). Here, the authors evaluated fluctuating asymmetry in three traits rather than one. In this study, a copulating male and a single male were collected at the same time and from the same location on the substrate. This is because as local groups of males compete for receptive females, the single male was likely to have been out-competed by the mating one. Interestingly, the relationship between fluctuating asymmetry and mating status differed in each species. In *D. simulans,* mating males actually showed elevated fluctuating asymmetry in both of the two years of the study. In controls, mating males of *D. pseudoobscura* showed the same comparatively lower fluctuating asymmetry as did mating males of *D. melanogaster* in the laboratory study. For *D. mojavensis,* fluctuating asymmetry did not differ between mating and single males. Thus in two *Drosophila* species, mating success was associated with low fluctuating asymmetry, while in the other two it was not. In fact in one species, mating success was associated with increased fluctuating asymmetry.

Similar association studies were subsequently conducted in male scorpionflies (*Panorpa japonica*) by Thornhill (76, 77), who reported that fluctuating asymmetry of successful mating individuals was comparatively lower. Harvey & Walsh (24) and Ligget et al (33) reported that in the damselfly *Coenagrion puella* and the dung fly *Scathophaga stercoraria,* respectively, males found in copula appear to have more symmetrical wings than do single males.

An important factor (24, 40) confounding interpretation of all cases in which mating males display greater symmetry is that one cannot know the relative ages of males in the mating and nonmating categories. *D. mojavensis* males require over a week to become sexually mature, which allows ample time for natural selection to remove developmentally unstable flies from the population. In the damselfly study, the authors raise the same question about the action of natural selection on maturing males before they return to mating sites. This concern applies to the other studies as well and must be addressed before the explanation of sexual selection can be invoked.

What are the ways in which developmental instability could be related to decrements in fitness? By definition, the phenotypic perturbations of interest are not large. Characters that are required for an organism's critical functions are usually extremely well canalized and hence quite symmetrical. Only one study (2) directly examined the influence of minor fluctuating asymmetries on performance traits. It was actually conducted to explore an alternative to the sexual selection hypothesis for fluctuating asymmetry in bird wings and tails (50, 51). The authors (2) presented convincing data that symmetry in bird tails and wings is under strong natural selection for aerodynamic efficiency, selection that acts far in advance of sexual selection. As this study has so nicely illustrated, natural selection can act directly on the asymmetries. In contrast, the measurable developmental instability in many traits may merely be correlated with some other feature of the organism's phenotype that itself reduces fitness.

Several contrasting hypotheses are available to explain the possibility that fluctuating asymmetry translates into reduced courtship success. One is that asymmetry indicates poor mate quality, forming the basis for sexual selection (50, 52). The importance of this factor may vary in different taxa. The poor mate quality hypothesis, regardless of whether the quality results from genetic or environmental factors, relies on the assumption that individuals actually assess symmetry itself in prospective mates. In other words, symmetry plays a role in mate choice, another phenomenon that is difficult to demonstrate. Alternatively, asymmetry can reflect or may be correlated with some other, less-than-optimal phenotypic state that puts the organism at a disadvantage with respect to natural or sexual selection.

With respect to the insect species in which symmetry is associated with mating success, the responsible mechanisms are unknown. The associations

could be generated by natural selection, or they could reflect the ability of females to discern between symmetry levels and then mate accordingly. As discussed above, this explanation assumes female choice, a phenomenon that is difficult to demonstrate with respect to any male character in insects. The most convincing case of female preference for symmetry was demonstrated in vertebrates with manipulated leg-banding colors in male zebra finches. Females of most insect species may not be capable of assessing the small symmetry differences in male structures during courtship. For example, we can imagine that differences in wing asymmetry would be more detectable to females than the differences in bristle number discussed above. Yet one study in which *D. melanogaster* male wings were clipped revealed no decrease in the courtship success of asymmetrical males (41). The fact that mating success is associated with bristle symmetry (40) does support the alternative explanation that fluctuating asymmetry reflects some other phenotypic state that influences males' ability to mate. Further support for this interpretation comes from the scorpionfly study in which pheromones from high compared with low fluctuating asymmetry males were reported to have detectably different effects on females (78).

In one study (39), fluctuating asymmetry in the structures or chemical processes of the central nervous system was proposed as the explanation for the subtle departures from normal behaviors of developmentally unstable organisms in a given species. Without inspection of the central nervous system, the structural or chemical asymmetries would go undetected as such. This model, known as behavioral phenodeviance, provides for a behavioral equivalent or extension of morphological asymmetries. These authors (39) argue that because behaviors are often the characters acted upon by natural or sexual selection, abnormal behavior could explain why developmental instability and reduced fitness are often correlated. Indeed, humans with schizophrenia, a behavioral disorder of complex etiology characterized by a severe fitness decrement, often have increased brain asymmetries (37). Recent observations on *D. melanogaster* (87) are also consistent with this model.

In summary, evidence in various systems supports each of the genetic models discussed for developmental instability. As none of the studies involve a direct test, such experiments should be a high priority. Possibly, direct tests could support all three models, and there is no reason why several genetic mechanisms could not contribute to developmental homeostasis. Different mechanisms could prevail in different species, depending upon their evolutionary histories and genetic architectures.

The underlying mechanisms have important implications for the relationship between fitness and developmental instability. For example, if developmental instability phenotypes, i.e. high fluctuating asymmetry, result from homozygosity for deleterious recessives, the offending alleles would be selectively

reduced in the population. If the most developmentally stable phenotypes (i.e. the most symmetrical) resulted from intergenic combinations of alleles, selection would favor the increase of coadapted complexes of genes. On the other hand, if heterozygosity (i.e. overdominance) produced the most stable (symmetrical) phenotypes, balancing selection would maintain genetic polymorphism. The importance of this distinction for sexual selection can be illustrated by the good genes model of mate choice. If, for example, asymmetry reflected a bad gene or combination thereof that could be passed to offspring, the outcome of female choice would be very different from the case where asymmetry resulted from homozygosity per se.

DEVELOPMENTAL INSTABILITY AND ECOLOGICAL STRESS

Just as with the genetic issues, a major concern here is whether ecological stressors can predictably disrupt development in ways that show up as developmental instability. If so, is developmental instability caused by factors that are linked to decreases in fitness? And how does genotype mediate the influences of environmental stressors during development?

As discussed in recent reviews (6, 21, 65a, 85), ecological stressors are assumed to cause developmental instability, and developmental instability is assumed to be related to reduced fitness. The validity of these assumptions must be assessed because they underlie emerging trends in several areas of evolutionary biology. For example, conservation biology represents one such area. Conservation biologists need a measure of when a population is at risk or when an environment poses a risk. Developmental instability, especially fluctuating asymmetry, is becoming the instrument by which such risks are typically evaluated (21, 30, 62). Thus, the concept of developmental instability has become the core element in an international environmental assessment effort known as BIOTEST (22). Because fluctuating asymmetry is also assumed to signal the phenotypic quality, as determined by the developmental environment, of prospective mates, fluctuating asymmetry is a focus of studies of sexual selection. With respect to conservation biology issues, risks may be genetic or environmental (e.g. when inbreeding results from a population bottleneck).The relationship between inbreeding depression and developmental instability was discussed above, but the application of this relationship to endangered populations has not yet offered consistent interpretations. For example, Wayne et al (85a) reported significant fluctuating asymmetry in cheetahs, known to be highly inbred and lacking in genetic variation. But their observations have been challenged by Kieser & Groeneveld (28a) on statistical grounds. Population bottlenecks have not yet been of concern for most insect

species, but this could change rapidly with the hastening of such processes as habitat destruction in the tropics.

Studies of environmental stressors on developmental instability have been as inconclusive as the bottleneck studies. Although several field studies appear to support a relationship between developmental instability and various pollutants in natural populations of vertebrates (1, 4, 58, 88) and plants (17), there have been few controlled laboratory studies on any of these species. However, invertebrates, especially insects, lend themselves well to this type of experimentation, so it is no surprise that the majority of laboratory studies have used insects, especially *Drosophila* spp.

Parsons (60) reported that elevated developmental temperature increased sternopleural bristle fluctuating asymmetry in *D. melanogaster,* but that phenylthiourea in larval diets did not (59). More recently, Graham et al (21a) exposed developing *D. melanogaster* to various concentrations of lead and benzene. Both chemicals caused an increase in fluctuating asymmetry of bristles and, at the highest concentration of benzene, directional asymmetry appeared to replace fluctuating asymmetry. Clarke & McKenzie (10) found that fluctuating asymmetry for bristles was a reliable indicator of density or temperature-induced stress in mass-reared sheep blowflies.

Drugs used to treat livestock for parasites are another group of chemicals that have been tested for their ability to disturb development. These chemicals appear in the feces of treated animals, exposing dung-feeding and -breeding insects to their potentially harmful effects. Australian bush flies, *Musca vetustissima,* grown in the feces of cattle treated with avermectin D, exhibited greater fluctuating asymmetry in two wing veins compared with wing veins of control flies (12). Sheep, in contrast, are treated with ivermectin, which is administered orally. When Wardhaugh et al (84) tested for increased fluctuating asymmetry in bush fly wing veins, they found no difference between flies from treatment and control (sheep) groups, despite an adverse effect of the drug on insect larval viability and wing size (KG Wardhaugh & RJ McMahon, unpublished data).

Natural populations face a range of ecological stressors including poor resources, extreme temperatures, parasites, and disease. All of these have been postulated to increase fluctuating asymmetry, decrease performance, and decrease mate quality (62), but few studies have sought to systematically demonstrate the validity of this assumption.

The most thorough study of ecological stressors and fluctuating asymmetry is that of Polak (64) on the cactophilic fruitfly *Drosophila nigrospiracula* and two of its natural parasites, an allantonematid nematode (species undefined) and a macrochelid mite (*Macrocheles subbadius*). Nematode infection occurs in the larval stage, and feeding by the parasite is associated with significant damage to the fly. Mite infection, on the other hand, occurs at the adult stage;

then, the parasite attaches, usually to the fly's abdominal wall and consumes the hemolymph of the host. Mites significantly reduce longevity of infected individuals (64) and mating success of males (65). Levels of fluctuating asymmetry for individuals parasitized by mites and by nematodes were compared with levels in uninfected flies. Not surprisingly, given that nematode infection occurs early and can disrupt development, this parasitization was associated with significantly elevated fluctuating asymmetry. Mite infection, on the other hand, was not. While mites cannot be expected to induce fluctuating asymmetry in individuals whose development is already complete, fluctuating asymmetry might be expected to be associated with mite parasitism if developmentally unstable flies were more susceptible to parasitism. This does not appear to be the case with *D. nigrospiracula.*

In conclusion, the literature reflects inconsistencies as to whether environmental stressors can impact fluctuating asymmetry, even when they clearly affect viability. Without further study, we cannot know if these differences in results reflect a problem with experimental design, i.e. lack of measurement error in studies with negative results, or if fluctuating asymmetry is simply not a consistent indicator of developmental history and thus of risk or quality.

CONCLUSIONS AND RECOMMENDATIONS FOR FUTURE RESEARCH

In the foregoing discussion, several issues have emerged that must be resolved. Clearly, genetic or environmental factors can cause increases in developmental instability, as measured by fluctuating asymmetry, but as yet we lack general principles as to exactly when these stressors will cause detectable effects. Before developmental instability can be reliably used in studies of evolutionary ecology, it must be more fully understood. The following list should be helpful to investigators wishing to participate in such an effort.

1. The role of the genotype in the genesis of developmental instability must be defined. Experiments should be designed to discriminate between the heterozygosity hypothesis and the coadaptation hypothesis. These studies should be done across taxa and should examine the impact of different breeding systems and selections histories on developmental instability. Greater detail regarding the genetic issues appear in the proceedings of the conference *Developmental Instability: Its Origins and Evolutionary Implications* (38). Only by comprehensive studies can a complete picture or set of principles be elucidated.
2. The role of nongenetic stressors in the genesis of developmental instability must also be defined. Graham et al (21) offer some excellent methodological guidelines. For example, is a given potentiator of developmental insta-

bility, say benzene, equally disruptive to all creatures? Are genotypes resistant to disruption by one stressor also resistant to others?

3. What is the connection between developmental instability, especially fluctuating asymmetry, and fitness? The nature of the selective forces (natural or sexual) should be carefully examined.
4. Methodological considerations should dominate the design of future studies. Negative data need to be reported, but only when measurement error has been part of the design and other statistical properties of asymmetry distributions are accounted for. In this regard, investigators should consult the primer prepared by Palmer (54) in designing new investigations.

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