GENETIC MODELS FOR DEVELOPMENTAL HOMEOSTASIS: HISTORICAL PERSPECTIVES

Charles M. Woolf [1] and Therese A. Markow[2]

[1] Department of Biology, Arizona State University, Tempe, AZ 85287-1501.
FAX: (480) 965-2519. Email: atcmw@asu.edu

[2] Department of Ecology and Evolutionary Biology, Biosciences West 310, PO Box 210088, University of Arizona, Tucson, AZ 85721-0088. FAX: (520) 626-3522.
Email: tmarkow@arl.arizona.edu

ABSTRACT

Three major models have appeared in the literature for the genetic mechanisms giving developmental homeostasis. A model based on the contributions of James F. Crow and Herman J. Muller states that Darwinian fitness (which includes developmental homeostasis) results primarily from the additive action of dominant alleles at various chromosomal loci. According to the Crow-Muller model overdominance plays a minor role, if any, for Darwinian fitness. I. Michael Lerner proposed a more elaborate genetic mechanism for developmental homeostasis consisting of (1) coadapted heterozygosity in complex polygenic systems and at a limited number of other loci, (2) coadapted homozygosity, and (3) coadapted interlocus interactions of alleles at loci in homologous and non-homologous chromosomes. A uniqueness of Lerner's model is his proposal that segregants of some of the coadapted highly heterozygous polygenic systems are phenodeviants. Although emphasizing the role of heterozygosity in some Mendelian populations, Lerner stated that no population can afford to have too many loci manifesting overdominance simultaneously. Unfortunately, Lerner's views on the importance of heterozygosity for developmental homeostasis are often represented incorrectly in the literature. While supporting the neoDarwinian view that homozygosity for specific alleles, combinations of alleles, and interlocus interactions of alleles are the essence of Darwinian fitness, Theodosius Dobzhansky in 1950 became a strong proponent of the additional importance of coadapted heterozygosity in the evolutionary process. A few years later, however, he became a spokesperson for the hypothesis that heterozygosity for many genes and gene complexes may produce higher fitness even without prior coadaptation. There is little evidence at present to support Dobzhansky's model for the importance of generalized overdominance in Mendelian populations, and there is no unequivocal evidence to rule against the Crow-Muller model. Lerner's model has not been fully tested. Answers are needed to the following questions to help decide between the Crow-Muller model and Lerner's model: (1) How often does overdominance occur in diploid species? (2) Do complex polygenic systems occur in Mendelian populations, maintained by heterozygote advantage, that have phenodeviants as segregants? (3) What is the true relationship between homozygosity in Mendelian populations and the presence of developmental instability? Creative research is needed to find answers

to the questions.

INTRODUCTION

Cannon (1932) in his book *Wisdom of the Body* presented the concept of homeostasis, which refers to the property of an organism to adjust itself to variable conditions. The word is often used in conjunction with an adjective, resulting in such combinations as physiological homeostasis, psychological homeostasis, ecological homeostasis, genetic homeostasis, and developmental homeostasis. The last mentioned example (developmental homeostasis) refers to the property of the organism to adjust, through self-regulation, to environmental or genetic disturbances during development and stay within the norms of development. Developmental homeostasis is often used interchangeably with the terms developmental stability and canalization (see below), although there is variation in definition and usage in the literature.

The antithesis of developmental homeostasis (developmental stability) is developmental instability. The presence of this book and the publication of a similar *book (Developmental Instability: Its Origins and Evolutionary Implications)* edited by Markow (1994), in addition to the increasing number of published papers during the past 15 years on the subject of developmental instability, attest to the growing interest in this important subject. The evolutionary significance and biological implications of developmental instability, sometimes manifested by fluctuating asymmetry, are addressed fully in the other chapters of this book, and as a consequence will only be given minimum coverage here. The emphasis of this chapter will be on the historical aspects of genetic models for developmental homeostasis.

Various different models for the genetics of developmental homeostasis have appeared in the literature during the past 50 years. Models that had a major impact are associated with the following names: James F. Crow, Theodosius Dobzhansky, I. Michael Lerner, and Herman J. Muller. The models are named here the Crow-Muller model, Dobzhansky's model, and Lerner's model. Neither Muller nor Crow specifically addressed developmental homeostasis in their writings. Muller's interests, among many others, were evolutionary biology and the genetics of Darwinian fitness. Crow, who

became the champion of the Crow-Muller model, shared these interests but also had specific interests in the genetics of heterosis. Although heterosis historically pertains to the vigor seen in hybrids, it is sometimes used interchangeably in the literature with developmental homeostasis in the sense that hybrids who manifest true heterosis will also manifest developmental homeostasis. Likewise, high Darwinian fitness is associated with developmental homeostasis. It is assumed that the genetic mechanisms for heterosis, high Darwinian fitness, and developmental homeostasis are similar, and this is implied in the writings of Lerner (1954, 1959), Dobzhansky (1950, 1952) and Dobzhansky and Levene (1955).

Dobzhansky presented a major model in 1950 concerning the importance of coadapted heterozygosity in the evolutionary process and for heterosis (developmental homeostasis). His views, however, changed with time. Lerner arrived on the scene in 1954 with the publication of an influential book (*Genetic Homeostasis*) giving a highly cited model for the genetics of developmental homeostasis. Unfortunately, the literature tends to give a misunderstanding of Lerner's views on the genetic mechanisms responsible for developmental homeostasis. This misunderstanding has led to a multitude of false statements in the literature as well as a multitude of experimental procedures to test hypotheses he never proposed. Suggesting that an author had not read the book he cites, or at least had not read it sufficiently carefully, Lerner (1961) commented, "Yet, were it not for his failure to follow the common custom of verifying before publication what the thesis he discusses actually was, he would not, I assume, have constructed and demolished a man of straw, under the curious illusion that this operation has something to do with proving or disproving the hypothesis that I proposed."

Lerner is often portrayed in the evolutionary biology literature as promoting the thesis that heterozygosity *per se* is advantageous, implying that Darwinian fitness is a function of the amount of heterozygosity that is present, and therefore the more chromosomal loci that are heterozygous, the higher the fitness. Lerner was never an advocate of this thesis. Because of this misunderstanding the developmental instability literature frequently portrays Lerner's views as being in opposition to the concept of genomic coadaptation, a term coined by Graham and Felley (1985) that appears frequently

in this literature (see papers in Markow 1994) where it is often associated with the name of Dobzhansky. The term genome historically refers to all the genes contained in a gamete, i.e. in a haploid set of chromosomes where each chromosome is a representative of a pair of homologous chromosomes (King 1968). Thus, a haploid organism has one genome, a diploid organism has two genomes, and a tetraploid organism has four genomes. The term genomic coadaptation can be defined, therefore, as the coadapted interactions of the genes in the genome or genomes present in an organism. The term coadaptation used by Dobzhansky, Lerner, and certain other biologists, refers to the mutual adjustments that occur in a gene pool by the action of natural selection to produce desirable outcomes. According to Lerner (1959) the process of coadaptation is probably a continuous one. A change in allelic frequencies at one locus by selection or by some other force results in a change of allelic frequencies at other loci. The secondary effect may in turn generate further changes in frequency at the original locus, until either the original balance is regained or a new one is achieved. The elements of the genetic system in the delicately balanced gene pool are, using Dobzhansky's (1950) term, *coadapted*. The interactions are epistatic when the contribution of an allele at one locus is affected by the contributions of alleles at other loci. Lerner was totally committed to coadaptation, stating that the components are (1) coadapted heterozygosity in complex polygenic systems and at a limited number of other loci, (2) coadapted homozygosity, and (3) coadapted interactions of alleles at loci in homologous and non-homologous chromosomes (i.e. coadapted interlocus interactions). Dobzhansky's often cited 1950 paper emphasizing the importance of coadapted heterozygosity in the evolutionary process and his prior publications promoting neoDarwinism, attest to his belief in the concept of coadaptation at that time in his life. However, a few years later he began to move away from this belief with the proposal that heterozygosity for many genes and gene complexes may produce higher fitness even without prior coadaptation. .

Our goal is to provide historical perspectives of the three major genetic models for developmental homeostasis associated with the names of Crow, Dobzhansky, Lerner, and Muller. With an understanding of these models, how they differ from each other, and what evidence exists to support or refute them, future tests of hypothesis can be more meaningful and lead to a greater understanding of

the consequences of the lack of developmental homeostasis.

GENETIC MODELS FOR DEVELOPMENTAL HOMEOSTASIS

In a series of publications, Waddington (see 1940, 1942, 1957) presented the concept of canalization (used interchangeably here with developmental homeostasis and developmental stability). Since stresses on developmental pathways or reactions by environmental factors and disruptive genotypes can result in variable phenotypes, he proposed that natural selection favors gene complexes that canalize (or buffer) these pathways or reactions against these disturbing forces so as to bring about one definite end-result. He visualized that the developmental pathways leading to the adult form is to a greater or less extent canalized (or buffered), and the biochemical reactions involved in each pathway are so interlocked, there is a tendency for the normal end-result to occur even if an earlier pathway has been disturbed by an environmental or genetic perturbation. Thus, by utilizing feedback mechanisms coadapted gene complexes are programmed to bring about constancy of the species and may succeed unless the consequences of the perturbations are too severe.

Waddington gave no genetic model for canalization, other than stating that it occurs because of biochemical feedback and cybernetic processes. Soon after the publication of Waddington's initial papers, Mather (1943) suggested that the coadapted gene complexes involved in canalization consist of linked combinations of polygenes with the constituent members balancing each other in action. Genetic recombination between existing combinations, resulting in new combinations of polygenes, allows adaptation to changing circumstances. Reference to this model appeared in the earlier literature on canalization, but it did not have a significant impact.

A. Dobzhansky and Overdominance

A major model for the genetics of developmental homeostasis was proposed by the prominent evolutionary biologist Dobzhansky, who helped usher in the neoDarwinian theory of evolution with the various editions of *Genetics and the Origin of Species,* and who pioneered the field of experimental

population genetics using *Drosophila pseudoobscura*. Prior to about 1950 Dobzhansky, as well as most other evolutionary biologists, affirmed that the presence of homozygosity for specific alleles, combinations of specific alleles, and interlocus interactions of specific alleles are the essence of Darwinian fitness. With the publication of a paper in 1950, Dobzhansky went on record as stating that coadapted heterozygosity is also a component of Darwinian fitness. After many years of studying inversions in *Drosophila pseudoobscura,* Dobzhansky reached the conclusion that the frequency of inversion polymorphism in this species is under the control of natural selection, with individuals heterozygous for these inversions having a higher Darwinian fitness than either homozygote (Dobzhansky 1948). He proposed there is selection for mutations at loci within the region of each inversion that result in overdominance (i.e., the heterozygote may be more fit then either homozygote because of the greater biochemical versatility of having the products of two alleles rather than the products of the same allele). In the key 1950 paper Dobzhansky concluded that inversion heterozygotes which carry two chromosomes derived from the same population have, as a rule, a higher fitness than either homozygote, while in contrast, inversion heterozygotes which carry two chromosomes of different geographic origin may not have this advantage. The hybrid vigor (i.e., heterosis) of the heterozygotes was ascribed to the interaction of alleles at loci in polygene complexes which have become *mutually adapted, or coadapted,* by natural selection in the course of the evolutionary process. Because of the lack of opportunity for coadaptation, offspring heterozygous for these inversions produced by parents from remote geographical regions should not normally show heterosis. Natural selection acts to promote the formation of a gene pool containing numerous loci, with many being closely linked both within and outside the inversion regions, resulting in coadapted heterozygosity (Dobzhansky and Spassky 1953). Dobzhansky and Levene (1955) tested the viability of individuals collected from a natural population of *Drosophila pseudoobscura*, homozygous and heterozygous for second chromosomes, when exposed to different environments. They concluded that the developmental patterns of the heterozygotes are better buffered against environmental disturbances than those of the homozygotes, and hence, heterozygosity for these chromosomes promotes developmental homeostasis.

Following the publication of his 1950 paper, an important event occurred that caused

Dobzhansky to move away from his conviction that all heterosis results from coadapted heterozygosity. The event was research carried out by Vetukhiv (1953) in his laboratory using *Drosophila pseudoobscura*. A detailed account of the relationship between Dobzhansky and Vetukhiv leading to the publication of this paper has been given by Lewontin (1987). Vetukhiv was a Ukrainian political refugee scientist whom Dobzhansky had taken into his laboratory. Vetukhiv's experiment was designed by Dobzhansky, who also interpreted the results and took the lead in writing the paper. In essence, Vetukhiv's experiments were Dobzhansky's experiments. Vetukhiv compared the viability under crowded conditions of F_1 and F_2 larvae when the parents were from the same population or from geographically remote populations. All parents were cytologically uniform and homozygous for the Arrowhead gene arrangements in the third chromosomes. The coadaptation model predicted that the F_1 intrapopulation hybrids should demonstrate more heterosis than the F_1 interpopulation hybrids, but the results did not conform to this model. The F_1 hybrids resulting from mating parents from different geographical regions exhibited significantly greater heterosis. It was then observed that the heterosis observed in the F_1 interpopulation hybrids did not carry over to the F_2 generation, presumably because of crossing-over and recombination. Dobzhansky was then forced to conclude (Lewontin, 1987) that there were exceptions to his coadapted heterozygosity model. In the Vetukhiv (1953) paper the statement was made that the data agree with the supposition of early students of heterosis that "heterozygosis is *per se*" a viability stimulant. Similar results were obtained by Brncic (1954), Vetukhiv (1954), Wallace (1955), and Wallace and Vetukhiv (1955). Wallace was a former student and prominent colleague of Dobzhansky. Brncic was an investigator from Chile who did his work in Dobzhansky's laboratory, under the supervision of Dobzhansky who also helped in the preparation of the manuscript. Dobzhansky then became an advocate of the advantage of non-coadapted heterozygosity at an undetermined number of loci in the gene pool of Mendelian populations. In a pivotal paper, appearing in 1955, Dobzhansky stated that although it is granted that heterosis may arise through a process of coadaptation, it may also occur for some other reason: "Genetic and even pre-genetic, literature contains a great, though rather confused, mass of evidence that hybrids between self-fertilizing strains of monoecius plants, as well as hybrids between quite distinct species, are luxuriant in one or more respects, by being larger, or faster growing, or more prolific than their parents. . . traits that

are sometimes, but not invariably, associated with fitness." He concluded, therefore, that heterozygosity for many genes and gene complexes may produce higher fitness even without prior coadaptation.

During the following years Dobzhansky moved further in the direction of a belief that alleles at loci throughout the chromosomes have the potential to demonstrate fitness overdominance. He was influenced by the research of Wallace, suggesting that newly arisen mutants in *Drosophila melanogaster* may be slightly heterotic (Wallace 1958, 1965; also see Stern et al. 1952 and Gustafsson, 1963), and that overdominance may be a function of genetic background (Wallace, 1963; also see Mukai, 1964, and Falk and Ben-Zeev, 1966). It is also certain that Dobzhansky was influenced by Lerner (1954), who presented the hypothesis in his book *Genetic Homeostasis,* that some Mendelian populations contain an obligate level of heterozygosity. As noted by Lewontin (1987) the concept of coadapted heterozygosity disappears from Dobzhansky's papers during the decade following the publication of the pivotal 1955 paper, except for a brief reappearance in Pavlovsky and Dobzhansky (1966), where, described by Lewontin, "it is like a glance, with a sigh, at the faded photograph of a long-dead sweetheart."

In his 1970 book *Genetics of the Evolutionary Process*, Dobzhansky devoted many sections to promoting the role of heterozygosity in the evolutionary process, arguing that many loci in Mendelian populations have the potential to show overdominance and that numerous heterotic multiple alleles at some loci is the rule. His evolving views on the advantage of non-coadapted heterozygosity are also demonstrated by his use of the terms euheterosis and luxuriance. In 1952 he distinguished between euheterosis and luxuriance, both sometimes occurring in the F_1 offspring of inbred parents. He defined euheterosis as true fitness heterosis resulting from a higher adaptive value of the heterozygote and luxuriance as that condition when the hybrids are larger, faster growing, having a greater seed set, or otherwise exceeding the parental forms in some quality. In that paper he said that luxuriance, from the evolutionary standpoint, is not adaptive. Instead, it is an accidental condition brought about by the complementary action of genes found in the parents. But by 1970 he had taken a more firm stand and equated luxuriance with heterosis, stating that, although it is not certain, luxuriance may be due to

heterozygosis for greater numbers of genes.

Although committed to the advantage of non-coadapted heterozygosity in the evolutionary process, Dobzhansky, in 1970, returned in a relatively brief discussion to his earlier inversion studies giving evidence for coadapted heterozygosity. Based on the research of Brncic (1954), Wallace (1955), and Kitagawa (1967) and his own convictions, he also reaffirmed that coadapted interactions among alleles at different loci throughout the chromosomes are another cause of increased fitness, suggesting that a gamete transporting a haploid set of chromosomes from a given population contains a coadapted system of genes, and this coadaptation is partly lost when some of the chromosomes of a set, or sections of a chromosome, are of different geographic origin.

B. Lerner and Coadaptation

In 1954 Dobzhansky acquired an influential ally in support of his proposition that overdominance is important for the evolutionary process. In his book *Genetic Homeostasis,* Lerner (1954) developed the thesis that some Mendelian populations, by the action of natural selection, acquire a high level of obligate heterozygosity at loci in polygenic systems, which become important genetic mechanisms for developmental homeostasis. Dobzhanky and Lerner were intellectual as well as close friends, often communicating with each other by letters written in the Russian language. Dobzhanky was born in Russia in the year 1900 and Lerner was born 10 years later in Harbin, China of Russian parents who had immigrated to that country. In a section (page 208) on genetic homeostasis in his book *Genetics of the Evolutionary Process* (1970), Dobzhansky makes the statement, "Lerner (1954) has analyzed this situation in a brilliant book." In 1970 one of us (CMW) was on sabbatical leave in Dobzhansky's laboratory at Rockefeller University in New York. One evening, while walking together near Central Park to a social occasion, Dobzhansky surprised him with the statement. "The two greatest living biologists are George Gaylord Simpson and I. Michael Lerner." Indeed, Dobzhansky had a great deal of respect for Lerner.

On page 108 of *Genetic Homeostasis*, in the section on the *Evolution of Buffering*

Properties, Lerner suggested that multiple heterozygosity in complex multigenic systems has a dual function in the life of Mendelian populations. (1) It provides a mechanism for maintaining genetic reserves and potential plasticity, and (2) it permits a large proportion of individuals to exhibit combinations of phenotypic properties near the optimum (i.e. it promotes canalization). Individuals who are highly heterozygous at the loci comprising these multigenic (polygenic) systems are buffered during development, and individuals who are highly homozygous at these loci may manifest phenotypic expressions consistent with lack of canalization. If the fraction of loci homozygous for specific alleles surpasses a threshold value, a given phenotypic expression, defined by Lerner as a "phenodeviant", may appear. A clear statement of the role of natural selection in creating these polygenic systems appears on page 108 of his book: **"**Clearly, the buffering properties of heterozygotes must be viewed as a manifestation of previous selection in a given genetic background, rather than as a phenomenon independent of the prior evolution of a population."

Lerner (1954) affirmed that he did not mean to imply that heterozygote advantage associated with these coadapted polygenic systems is the sole mechanism by which canalization occurs. He cited examples in *Drosophila*, poultry and other organisms suggesting the presence of overdominance at single loci, indicating that there may be situations when the heterozygous state at a single locus has a higher selective value than either homozygote state. He also acknowledged that modifiers of self-regulation may exist and based on the work of Wallace et al. (1953) he noted there is evidence that epistasis plays a role in determining viability. He additionally emphasized that organisms reproducing by cross-fertilization and self-fertilization are subjected to selection pressures of an entirely different nature. Because homozygosity is enforced under self-fertilization, except in the case of balanced systems, self-fertilized plants must have evolved in the direction in which homozygosity of certain alleles leads to greater adaptation. Thus, evolutionary history determines the nature of the coadaptation mechanisms present in any given species.

In a follow-up book, *The Genetic Basis of Selection*, Lerner (1959) commented that "the evolutionary significance of the concept of coadaptation cannot be over-stressed. . . it is based on

selective processes which build up and maintain a gene pool of alleles acting in a synergistic manner to produce desirable genotypic combinations." It was his view that coadaptation exists on two levels, interchromosomal and intrachromosomal, with the interchromosomal level referring to interdependences of alleles or more complex structures on non-homologous chromosomes, and the intrachromosomal level dealing with single loci and with segments and arms of a particular chromosome. On the intrachromosomal level, coadaptation may be of two kinds, *internal* and *relational*. The internal kind relates to the accumulation of alleles at neighboring loci or along a chromosome segment, while the relational kind refers to the optimal combinations not along a stretch of a chromosome but between homologous loci in the diploid state. Heterozygosity at a locus maintained by natural selection (i.e., overdominance) is a form of relational coadaptation. When favored by natural selection, homozygosity for a dominant fitness allele at a locus is also a form of relational coadaptation. Thus, it was Lerner's view that coadapted heterozygosity in complex polygenic systems, a form of relational coadaptation, is only one component of coadaptation.

During the years 1949-1953, one of us (CMW) was a graduate student at the University of California in Berkeley, where he attended courses and seminars offered by Lerner and during one summer served as a graduate research assistant on an NSF sponsored project, with Lerner as one of the principal investigators. These were formative years for the development of Lerner's hypotheses concerning developmental homeostasis, and Lerner shared his views with graduate students in both formal and informal situations. It was evident to graduate students, from all conversations, that the sporadic and ubiquitous presence of phenodeviants in different Mendelian populations and the genetic aspects of phenodeviants were the main impetus for Lerner to develop his coadapted heterozygosity model. One of these phenodeviants (crooked-toes) in poultry had been studied by him and one of his graduate students (Hicks and Lerner, 1949). In 1948 a paper by Dubinin on extra wing veinlets in *Drosophila melanogaster* appeared in a Russian journal. Lerner was highly intrigued with Dubinin's paper because it indicated that the genetic aspects of extra wing veinlets in *Drosophila melanogaster* were similar to those for crooked-toes in chickens. Lerner translated this paper from Russian into English, and a copy was made available to interested persons, including graduate students. In

discussions with students, and in answer to inquiries, Lerner was also quick to affirm that plants tending to be highly homozygous because of self-fertilization, plants having important haploid phases, and species with haploid males and diploid females, would not be expected to manifest complex heterozygous homeostatic systems. Instead, selection pressures in these types of organisms would have led primarily to the presence of homozygosity or hemizygosity for fitness alleles and coadapted interlocus interactions of alleles as buffering mechanisms.

Even though Lerner was a strong advocate of coadaptation, he is often cited as having a different view. In one response (Lerner 1961), he stated: "I have been represented as holding the view that balanced polymorphism is the situation to be found at all loci, in all populations of all species, at all times. On the contrary, I have repeatedly pointed out that no population can afford to maintain too many heterotic loci or blocks simultaneously. Furthermore, a concrete model of temporal succession of balanced polymorphisms is outlined in detail on p. 113 (of *Genetic Homeostasis*). " In his typical self-effacing manner, he also commented (Lerner 1961), "Granted, that by injudicious usage of such terms as "heterozygosity *per se*" and "obligate level of heterozygosity," I have provided infinite opportunities for quoting me out of context as espousing one or another view." Lerner used the term "heterozygosity *per se*" on page 67 of his book in a discussion (see below) of two speculative models of gene action within a coadapted polygenic system, without any intention of implying that ubiquitous heterozygosity is advantageous. Part of the misunderstanding is the layout of his 1954 book and lack of clarity of some of the sections. . For example, although he referred to the role of natural selection throughout the book, it was not until the last section of the book (page 102) that he made a definitive statement about his commitment to coadapted heterozygous buffering systems. Being an evolutionary biologist, he undoubtedly assumed that his readers understood his views on this subject. Key sentences are sometimes almost hidden in the middle of paragraphs, where they might be overlooked, and some statements appearing without clarification in a paragraph may give the wrong impression until it is realized that they are a follow-up to a topic discussed previously.

A major misunderstanding also results from Lerner's enthusiasm for his proposal that coadapted

heterozygosity in complex polygenic systems is important for developmental homeostasis in some Mendelian populations. His presentation of the proposal and his defense of the proposal resulted in a greatly reduced discussion of the importance of other components of coadaptation (i.e., coadapted homozygosity and interlocus interactions). He undoubtedly assumed that his readers would understood his neoDarwinian views of the importance of these other genetic systems, and therefore a detailed elaboration was not needed. Because of this imbalance, a reading of the book that is less than attentive, may lead to a false conclusion concerning Lerner's views on this subject. His views of the genetic mechanisms accounting for coadaptation are presented with balance and clarity in his 1959 book (*The Genetic Basis of Selection*). On page 101 he stated that many writers have attributed to him the claim that heterozygosity is the factor *uniquely* responsible for developmental homeostasis, in spite of his explicit statements to the contrary (in *Genetic Homeostasis*). In this book he also expressed his commitment (page 103) once again to the presence of coadapted buffering systems: "Finally, overdominance and heterosis must not be viewed as properties that have arisen fortuitously. When they exist within Mendelian populations, they do so by virtue of prior selection."

In a thought provoking presentation of *temporal succession* in Mendelian populations, Lerner (1954) postulated that a polygenic buffering system may evolve by a sequence of events at the loci comprising the system, whereby heterozygosity is replaced by homozygosity, if dominant genes are favored, or homozygosity is replaced by heterozygosity, if overdominance is favored. Through mutation pressure more efficient alleles would be integrated into the system, and the coadaptation process involving that polygenic system would be accompanied by coadaptation at other loci elsewhere in the chromosomes. By this process of succession a developmental homeostatic system in a species may evolve from one based mostly on homozygosity to one based on homozygosity and heterozygosity, and vice versa. The evolutionary history of the species would determine what system is present, and variation would be expected among species, but as he emphasized in 1961, no population can afford to have a genetic system for developmental homeostasis based too heavily on heterozygosity.

Three phenodeviants (crooked-toes in poultry and extra veinlets and podoptera in Drosophila

melanogaster) were discussed in detail by Lerner (1954), and he proposed that each shows multigenic inheritance, with the trait appearing when a threshold number is reached for specific alleles at the multiple loci comprising the system. That number can be reached by selection for the trait, or by inbreeding, resulting in increased levels of homozygosity for the responsible alleles. In addition to crooked-toes in poultry, and extra veinlets and podoptera in *Drosophila melanogaster*, Lerner (1954) listed other traits in various different organisms that are potential phenodeviants. It was Lerner's premise that depending upon the evolutionary history, a Mendelian population may have one or more coadapted highly heterozygous polygenic systems resulting in buffering during development. What phenodeviant appears following inbreeding depends on what alleles are present in a given polygenic system in a given species. However, some coadapted polygenic systems may not have obvious phenodeviants as segregants, indicating that homozygosity for certain alleles comprising polygenic systems, although resulting in lack of buffering, and therefore causing developmental instability, may not result in a phenotype that can be identified as a distinct phenodeviant.

On pages 63-73 Lerner (1954) turned his attention to a speculative subject of gene action leading to buffering during development. Following a discussion of buffering by feedback mechanisms in biochemical pathways, Lerner suggested that heterozygous buffering systems involve alleles with different functions, rather than being mutant hypomorphs or amorphs of wild type genes. He then presented two different models for gene action in highly heterozygous polygenic systems leading to buffering (canalization) and the possible appearance of phenodeviants. It should be pointed out that the lack of clarity of parts of this section, which Lerner (1961) admitted, as well as Figure 7 on page 67, have led to a misunderstanding of Lerner's views. In the first model, which he suggested is the classical biochemical model, *the alleles at each locus have an indispensable function.* In the second model *the alleles at each locus are interchangeable in their effects.* According to this second model an organism can afford to be homozygous at locus A, for example, as long as it is heterozygous at locus B. Which loci are heterozygous and which are homozygous does not matter in this system. Buffering will occur if a certain percentage of the loci are heterozygous. Thus, it is heterozygosity *per se*, that is important in this system, rather than heterozygosity at specific loci. Using upper case and lower case

letters to symbolize these alleles, with no implication of dominance, heterozygosity at all loci in the polygenic system (such as AaBbCcDdEe, etc.) produces the highest degree of buffering. Homozygosity at one or a few of the loci may keep development within the confines of the normal channel, but additional homozygosity results in poor canalization. Excessive homozygosity for specific alleles comprising the system, such as those symbolized by lower case letters (a, b, c, d, e, etc..) may result in the appearance of a specific phenodeviant. Lerner commented that the obvious difficulty with this second model is that it is impossible to verify, and there is no basis for the complete acceptance or the total rejection of the two alternative models. He suggested that what we know about the role of genes in biochemical pathways gives credence to the first model, but the complete overlapping of phenotypes for polygenic traits when genotypes are different supports the second model. Lerner concluded by saying that it is most likely that both types of gene action occur. It is of historical interest that this discussion of speculative gene action within a polygenic system led to the many incorrect citations in the literature that Lerner was a proponent of the advantage of heterozygosity *per se*.

Lerner (1954) was not the first author to use the term heterozygosity *per se*, or a phrase with a similar meaning. In 1948 Crow used heterozygosity *per se* to imply that loci exist at which the heterozygote is superior to the homozygote. The expression "heterozygosis is *per se* a viability stimulus" appeared in Vetukhiv (1953) and the term heterozygosity *per se* appeared in Vetukhiv (1954) who suggested that generalized overdominance may contribute to heterosis. In the 1955 pivotal paper Dobzhansky said "Various genetic and physiological mechanisms through which heterozygosity *per se* could produce heterosis have been discussed by Lerner (1954) and others." But of course, as described above, Lerner used the term heterozygosity *per se*, not to imply the developmental advantage of ubiquitous heterozygosity, but as a possible mechanism of gene action within a polygenic system.

C. The Crow-Muller Model

In 1955 when Dobzhansky announced his belief that heterosis may arise by a process other than coadaptation, he also contrasted the "balance" hypothesis, that he championed, with a "classical hypothesis" attributed to Muller but named and described by Dobzhansky. Crow (1987) gave a highly

informative historical account of this situation and the long lasting controversy involving Dobzhansky and Muller concerning the importance of overdominance in the evolutionary process

In the characterization of his balance hypothesis, Dobzhansky presented his proposal for the selective advantage of heterozygosity in Mendelian populations stating that the adaptive norm is an array of genotypes heterozygous for more or less numerous gene alleles, gene complexes and chromosomal structures. The advantage of the multiple heterozygotes results in a balanced system, with recombination and segregation resulting in homozygotes that are more or less inferior to the norm in fitness. Because of the complexity of the gene complexes, including multiple alleles at many of the loci, homozygotes may occur infrequently. The populations acquire a high level of obligate heterozygosity and evolutionary changes will not be limited to simple allele substitutions. Instead these changes will alter the whole genetic system and provide a re-patterning of the gene pool of the population. The presence of overdominance at many loci is the framework of Dobzhansky's balance hypothesis.

The classical hypothesis, attributed to Muller by described by Dobzhansky, gives no importance to the role of overdominance. "According to the classical hypothesis, evolutionary changes consist in the main in gradual substitutions and eventual fixation of the more favorable, in place of the less favorable, gene alleles and chromosomal structures. Superior alleles are established by natural selection, and supplant inferior ones. Most individuals in a Mendelian population should, then, be homozygous for most genes. Heterozygous loci will be a minority." Heterozygosity in a population occurs because of (1) recurrent mutation at each locus coupled with the interaction of selection, (2) the presence of genetic variants which are adaptively neutral, or which possess slight adaptive advantages at some times in some places, (3) adaptive polymorphism maintained by the diversity of habitats occupied by the population, and (4) the rare good alleles which have not had time to displace their alleles.

With the publication of his 1955 paper, Dobzhansky ushered in a debate over the genetic load of a population, and primarily the genetic load of the human population. A question then became, "What is the comparative genetic load on a population under the assumptions of the balance and

classical hypothesis?" Crow (1958) defined the genetic load of a population as the extent to which the fitness of a population is impaired by the fact that not all individuals are of the optimum type. The genetic load has components. One, the *mutational load*, is the extent to which the fitness of a population is diminished by recurrent mutation. It could be measured, in theory, by comparing the fitness of a population that would be obtained if recurrent mutation were zero and gene frequencies were in equilibrium. Another component is the *segregational load*, which is present when selection favors the heterozygote, and is the extent to which the fitness of a population is reduced by the presence of segregants (such as Lerner's phenodeviants). Again, it could be measured, in theory, comparing the fitness of a population that would be obtained if advantage of the heterozygote did not exist and gene frequencies were in equilibrium.

In 1950 Muller published a classical paper with the title "Our load of mutations." In the period following World War II there was great concern about the effects in human populations of radiation from atomic bomb testing and other technological sources. In his paper he argued that increased exposures to radiation would increase the rate of mutations in the human population, and the vast majority of the radiation caused mutations would be deleterious. To the contrary, Dobzhansky proposed that less favored alleles could be maintained in Mendelian populations by selection for the heterozygote. Dobzhansky also took the stand that the advantage of heterozygosity in the evolutionary process tends to minimize the threat of a slight increase in mutation rate caused by radiation, and even suggested (Wallace and Dobzhansky, 1959) that such an increased mutation rate could be beneficial in some situations by increasing heterozygosity and replacing heterotic alleles that might have been lost by genetic drift, a proposal that was, of course, an anathema to Muller. Because of the segregational load problem, the supporters of the classical hypothesis argued that too much coadapted heterozygosity in a Mendelian population, and specifically the human population, may impose too heavy of a genetic load, in fact the load may be heavier than the population can bear. In consonant with this argument was Lerner's view (1961) that no population can afford to maintain too many heterotic loci or blocks simultaneously.

Since wild type alleles in natural populations tend to be dominant, it was Muller's view that dominant alleles are therefore the superior alleles in the fitness sense. Hence, the classical hypothesis, attributed to Muller by Dobzhansky, soon become synonymous with the *dominance hypothesis*, and with the emphasis on overdominance, the balance hypothesis, favored by Dobzhansky, soon became synonymous with the *overdominance hypothesis* (Crow 1987).

The dominance hypothesis also had support from hybridization studies with cultivated plants. A history of the development of ideas concerning hybrid vigor is given in Gowen (1952), and an overview is presented by Crow (1987). The Mendelian concept that hybrid vigor is a consequence of heterozygosity was reached independently in 1908 by Shull and East (see Gowan 1952), and it was Shull, while lecturing in Germany in 1914 three weeks before the outbreak of World War I, who coined the word heterosis as a substitute for "stimulation of heterozygosis" (see Shull, 1952). The observed heterosis in the F_1 progeny of matings of parents from different inbred lines led to the acceptance of the overdominance hypothesis by many plant and animal breeders, but acceptance was not complete. Bruce (1910) and Keeble and Pellew (1910) suggested that hybrid vigor might result from the covering of deleterious recessive genes by dominant genes. During the next 40 years both the overdominance hypothesis and the dominance hypothesis had supporters among plant and animal breeders. In reviewing the history of the development of each model for heterosis in cultivated plants, Crow (1948, 1952) stated that the dominance hypothesis attributes the increased vigor of heterozygosity in F_1 progeny to the covering of deleterious recessive alleles by their dominant alleles, while the overdominance hypothesis assumes that loci exist at which the heterozygote is superior to either homozygote. In defense of the dominance hypothesis he noted that most mutations observed in *Drosophila* and in other organisms are recessive and almost all are deleterious. He also noted that experimental studies have shown that populations contain a large number of detrimental recessives, and hence inbreeding leads to a loss of vigor by causing homozygosity of these recessives alleles. Since dominant (wild type) alleles tend to be beneficial to the organism, matings between individuals from random inbred lines allow dominant alleles to cover the deleterious recessives in the F_1 progeny. He concluded that the dominance hypothesis is adequate to explain the loss of vigor that results from

inbreeding and the recovery that occurs following outcrossing, but he also added, that it is difficult to explain how hybrids can exceed, in some cases, the fitness observed in the parental populations. And hence, among other possibilities, he concluded that it appears likely in these cases that a small proportion of the heterosis results from overdominance.

In 1952 Crow presented assumptions for the dominance hypothesis for heterosis, based on observations in maize and other cultivated crops: The alleles concerned with vigor are dominant and there is additivity of effects among loci. There are no barriers to recombination, even though close linkage may be present among some loci that would prevent each dominant allele from reaching its own equilibrium frequency independently of other loci. Maximum heterosis occurs when each involved locus contains at least one dominant allele, but because of the presence of recessive alleles in populations, for one reason or another, maximum heterosis is rarely achieved.

Crow (1987) opposed Dobzhansky's views that overdominance exists at a majority of loci and a mutation at any given locus has the potential of being heterotic. His reasons were as follows: (1) Experiments giving evidence that overdominance can be mimicked by pseudodominance, i.e., the presence of close linkage of dominant genes and deleterious recessive genes (i.e., A b/a B). (2) The observation that some inbred strains of maize, produced by selection, are nearly as good as former hybrids. (3) The lack of convincing evidence that isozyme polymorphisms observed in a natural population are maintained by overdominance. Perhaps only a small proportion of loci, if any, manifest overdominance. (4) Inability to confirm unequivocally some of the results of experiments using Drosophila, especially those dealing with synthetic lethals, carried out by Dobzhansky and his associates in support of overdominance. (5) With few exceptions, such as the "overworked" sickle cell anemia example by teachers of biology, there has been a failure to find clear-cut examples of overdominance among the vast numbers of spontaneous mutations that have been studied in various organisms. (6) Among loci that lend themselves to isozyme studies, the average percent that are heterozygous (about 10 percent) in various organisms is closer to Muller's estimate than Dobzhansky's, even though these enzyme studies give no estimate of the amount of heterozygosity in repeated sequences, or in the vast

amounts of DNA that are not translated. (Traditional enzyme studies also give no estimate of the amount of heterozygosity present at the loci in polygenic systems with the alleles [modifiers] acting additively.)

Crow (1987) concluded: "All these arguments provide conclusive evidence against Dobzhansky's view of overdominance at the majority of loci. Overdominance is now relegated to a position of much less, perhaps very little, importance. Again. Muller was more nearly correct."

Wright's, (1931, 1940) model of the consequences of the subdivision of a large Mendelian population into semi-isolated subpopulations of varying sizes and occupying different environmental niches gives an explanation for additional genetic variation in a population, other than that occurring from recurrent mutation. In such a population all four forces of evolution come into action: mutation, selection, genetic drift, and migration. Recurrent mutation provides the building blocks for evolutionary change. Genetic differentiation of the subpopulations will be adaptive (action of natural selection) and non-adaptive (action of genetic drift in small subpopulations and of migration introducing non-coadapted alleles into a subpopulation). Complete fixation or loss of alleles by genetic drift may be prevented in a small subpopulation because of the action of migration. A subpopulation may experience a decrease in size and go through a genetic bottleneck, resulting in a loss of alleles, and as a result the gene pool may be partially out of tune with its environment when the subpopulation increases in size. Some of the subpopulations may be eliminated by natural selection, while others may flourish. When a successful subpopulation grows large and expands its territory, it may be subdivided again into partial isolates. A large Mendelian population with such a background contains the potential for a wealth of genetic variation, allowing natural selection to be effective. With a history of genetic drift or genetic bottlenecks, or the action of natural selection in former ecological niches occupied by the population, a Mendelian population may also be almost fixed for a series of suboptimal alleles affecting fitness.

Explanation for Luxuriance According to the Crow-Muller Model: The presence of homozygosity for suboptimal alleles in established Mendelian populations because of its past history

(Morton et al. 1967) gives one explanation for the luxuriance observed in the Vetukhiv (1953, 1954) studies and discussed by Dobzhansky (1955, 1970). Populations with a history of genetic drift or a genetic bottleneck may be almost fixed for suboptimal alleles at various loci. Parents from different Mendelian populations that are homozygous for suboptimal alleles at different loci may produce F_1 luxuriant hybrids because the suboptimal alleles are covered by optimal alleles (i.e. aaBBccDD x AAbbCCdd –> AaBbCcDd). The overall luxuriance observed in the F_1 hybrids is not expected in the F_2 generation because of the recombination effect. Similarly, Mendelian populations may also be almost fixed for certain suboptimal alleles because of the action of natural selection in former ecological niches occupied by the populations, where those alleles were optimal. If the loci containing these suboptimal alleles in a given population are different from those in a geographically removed population, matings between members of these Mendelian populations complementation will result in luxuriant F_1 hybrids, with recombination causing this effect to disappear in the F_2 generation.

Explanation for Lerner's Phenodeviants According to the Crow-Muller Model: The Crow-Muller model for developmental homeostasis specifies that the phenotypic variants described as phenodeviants by Lerner (1954) are not segregants from polygenic systems maintained in Mendelian populations by advantage of the heterozygote. Recurrent mutations at polygenic loci and at major loci in the evolutionary history of a Mendelian population, in which genetic drift and migration may have played roles, allows for a vast amount of genetic variation for traits with a polygenic basis and for traits due to semi-dominant genes which show a low penetrance in the absence of polygenic modifiers. Selection for these traits, or close inbreeding over many generations, would give the results summarized by Lerner (1954), according to the Crow-Muller model.

COMPARISONS OF THE MODELS

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The Crow-Muller model (i.e., the classical model or dominance model) specifies that developmental homeostasis results primarily from the interaction of dominant fitness alleles, with natural selection favoring homozygosity and a coadapted interlocus interaction of these alleles.. Although

Muller acknowledged that being heterozygous for the Hemoglobin S allele, resulting in the presence of sickle cell hemoglobin, is advantageous in an environment infested with malaria, he viewed this situation as a rare exception and held the view that in general overdominance plays no role in the evolutionary process. Crow (1987) was less adamant and allowed that it might be present at a minority of loci. An appropriate statement, therefore, is that Crow-Muller model gives little, or no importance to the role of overdominance.

Although Dobzhansky was a proponent of coadaptation in 1950, his views soon evolved to accept the additional importance of generalized overdominance in the evolutionary process and therefore for developmental homeostasis. In contrast to the Crow-Muller Dominance Model, Dobzhansky's model (post 1955) can be expressed as the Overdominance Model.

The components of coadaptation in Lerner's model consist of coadapted heterozygosity, coadapted homozygosity, and coadapted interactions of alleles at loci scattered throughout the chromosomes. Although Lerner's model emphasizes the advantage of heterozygosity, it was his view that no population can afford to maintain too many heterotic loci or blocks simultaneously. Lerner's model is unique because it proposes that the segregants of some coadapted highly heterozygous polygenic systems are phenodeviants.

The differences among these three models provide opportunities for testing them, but similarities among them and the features of Lerner's overall model present challenges.

A. Testing for Phenodeviants

The existence of phenodeviants, as segregants of highly heterozygous polygenic systems maintained by heterozygous advantage, is an essential feature of Lerner's model. Tests are needed to determine if phenodeviants actually occur in Mendelian populations, including human populations. It is of interest that since the publication of Lerner's book in 1954, the literature is void of attempts to test appropriately the phenodeviant hypothesis in *Drosophila melanogaster* and other laboratory species.

Creative research will be required to demonstrate that a candidate trait meets the genetic criteria for a phenodeviant, and especially that the responsible alleles are maintained in the population by selection for the heterozygote. Lerner's model for developmental homeostasis will gain immediate acceptance if future studies show that phenodeviants are a reality.

B. Inbreeding, Homozygosity, Developmental Instability, and Fluctuating Asymmetry

Inbreeding and Homozygosity: Inbreeding in Mendelian populations resulting in high levels of homozygosity characteristically results in individuals showing a loss of vigor. All three models assume that homozygosity for deleterious recessive alleles present in the population will be a cause of inbreeding degeneration. Lerner's and Dobzhansky's models assume that an additional reason for inbreeding degeneration is homozygosity for suboptimal alleles at polygenic loci and other loci that are maintained in the population by heterozygote advantage. With an emphasis on the importance of heterozygosity, Dobzhansky's and Lerner's models assume that individuals who are highly homozygous because of inbreeding should exhibit reduced vigor. Mather (1973) has emphasized, however, that inbred homozygotes from normally outbreeding species range widely from being very poor in vigor to others which are as vigorous as heterozygotes. Thus, he said, "gene content must therefore be important as well as heterozygosity." Crow (1987) has also pointed out that certain inbred lines of maize produced by selection are as vigorous as former hybrids. Geneticists who routinely make isogenic stocks of *Drosophila melanogaster*, and maintain them by brother-sister matings, also observe great variation in vigor among strains, with the variation being a function of the genes they possess. However, even the most successful of these strains has not been shown to be competitive with natural wild type strains regarding reproductive fitness, indicating that the role of overdominance cannot be dismissed. Lerner (1954) has also noted that depending on the mating scheme used, natural selection may force the maintenance of heterozygosity at a few loci in inbred lines. Nevertheless, because of the emphasis placed on heterozygosity by Dobzhansky and Lerner, the overall observations showing the relative success of some homozygotes favors the Crow-Muller model. The success of some homozygotes especially rules against Dobzhansky's model because of his emphasis on the importance of overdominance in Mendelian populations, as outlined in his balance hypothesis. The situation is less

definitive, however, for Lerner's model which states that coadapted heterozygosity is only one component of coadaptation. His succession scheme (Lerner 1954) implies that variation exists among Mendelian populations in their dependencies on levels of heterozygosity in their buffering systems. As a consequence, species A may tolerate higher levels of homozygosity, following inbreeding, than species B. Genetic variation may also be present within a species for the other components of coadaptation (coadapted homozygosity and coadapted interlocus interactions). This genetic variation allows for the possibility that as inbreeding proceeds these components, or adjustments in them, may provide the vigor needed for survival. As summarized by Lerner (1959): "If the population is to survive, it must have or develop an increased tolerance to inbreeding and attain a reintegration of genetic structure."

Relationships of Inbreeding, Homozygosity, Developmental Instability and Fluctuating Asymmetry: With the exceptions of directional asymmetry and antisymmetry (see Palmer 1994) the genotype of a bilateral organism is programmed to make one side of the body identical to the other. Even in the presence of developmental homeostasis the potential of the genotype is rarely achieved, with minor differences occurring between sides because of the influence of stochastic events (developmental noise) during development, resulting in fluctuating asymmetry. Fluctuating asymmetry is defined as random deviations from symmetry in either direction so that the sum of the deviations is zero (Van Valen 1962; Palmer 1994). An intriguing morphological manifestation of developmental instability (i.e. lack of developmental homeostasis) is increased fluctuating asymmetry, defined as a level of fluctuating asymmetry above that resulting from developmental noise. As discussed in the chapters of this book and elsewhere (see papers in Markow 1994; also see references in Markow 1995) increased fluctuating asymmetry, as a manifestation of developmental instability, may occur for many different reasons, including inbreeding degeneration, homozygosity for deleterious recessive alleles, presence of certain dominant mutant alleles, deleterious gene combinations, aneuploidy, chromosome aberrations, and various different stressors in the environment. Disrupting the genetic composition of coadapted gene complexes by inbreeding or selecting for traits so that buffering potential is diminished, may increase the likelihood of developmental instability, resulting in increased fluctuating asymmetry. Matings between individuals of different species may also result in hybrids with disabled buffering systems, resulting in

developmental instability and increased fluctuating asymmetry. This potpourri of effects suggests that various stresses during development, whether genetic or environmental, may override the genetic mechanisms trying to maintain developmental homeostasis.

Some reports in the literature support the hypothesis that developmental instability, resulting in increased fluctuating asymmetry, is associated with inbreeding and homozygosity, but others find no evidence for this relationship (reviewed in Markow 1995). In a provocative discussion in which he questions our understanding of the impact of inbreeding on developmental homeostasis and Darwinian fitness in human populations, James V. Neel (1991) commented in a letter to one of us (TAM) that if our general thesis about the level of inbreeding in tribal populations can be extended to the pre-tribal stages of human evolution, which is a legitimate extension, then human evolution has occurred in the face of a very high level of inbreeding. Thus, if developmental instability is associated with inbreeding, much of human evolution has occurred under conditions of disturbed developmental homeostasis.

Because of the relatively low inbreeding coefficients found in most urban human populations it is expected that levels of fluctuating asymmetry of traits would not be different in random individuals resulting from consanguineous and non-consanguineous matings. This was shown by the studies of Niswander and Chung (1965) and Dibernardo and Bailit (1978). However, increased fluctuating asymmetry has been reported in small highly inbred communities (Livshits and Kobyliansky, 1991). Stressors in the environment may have an influence in a small isolated community, and there is always a question whether the observed increased fluctuating in a small highly inbred community is the result of increased homozygosity in buffering systems or because of the presence of suboptimal recessive alleles specific to that community, perhaps because of a founder effect, made homozygous by inbreeding. Additional isolated communities from various different parts of the world, with high coefficients of inbreeding, need to be studied.

To obtain additional information about the relationships among homozygosity, developmental instability and fluctuating asymmetry, *Drosophila melanogaster* would be a good species to study

because of the opportunity of establishing isogenic stocks with chromosomes from different strains. Studies of *many different* isogenic strains should yield information on whether increased fluctuating asymmetry is associated with increased homozygosity or with homozygosity for specific suboptimal alleles (i.e., deleterious recessive alleles). Studies of isogenic strains maintained by brother-sister matings, as well as by random matings, and noting comparative changes in these strains with passing generations, using the tool of fluctuating asymmetry, should provide evidence for or against Dobzhansky's model, and test the various aspects of Lerner's model, including the phenodeviant hypothesis.

According to Lerner's model, coadapted heterozygosity would not be expected to play a major role for developmental homeostasis in species that are normally self-fertilized (and thus highly homozygous), in haploid species, in plants with a prominent haploid phase, and in species with haploid males and diploid females, such as ants and honeybees. In these organisms homozygosity for fitness alleles and coadapted interlocus interactions would be expected to be the prime genetic mechanisms for developmental homeostasis. In a study of ants (Iridomyronex humilis) with multiple queen colonies, Keller and Passera (1993) found that the level of fluctuating asymmetry of workers produced by inbreeding queens was not significantly higher than that workers produced by non-inbreeding queens, a result that would be predicted by the Lerner model. Likewise, Clarke et al (1992) observed in a study of honeybees (*Apis mellifera*) that increasing homozygosity in females by inbreeding for six generations did not increase the level of fluctuating asymmetry of wing characters in these females. The males consistently showed higher levels of fluctuating asymmetry than females, which the authors suggest may be due to dosage compensation. Thus, females (diploids) by having two copies of each gene are better able to maintain normal development than males (haploids) with only a single copy. A complication is the degree of polyploidy that occurs in somatic tissues in both drone and worker honeybees. Although during first instar the cells of drones are haploid and those of workers are diploid, polyploidization may occur in later instars in both drone and worker somatic tissues (Risler 1954), with variation occurring among somatic cells. For example, in drone somatic cells, leg imaginal discs become diploid at the second instar, but antenna imaginal discs remain haploid-- neuroglial cells become diploid at the second

instar but neuroblasts remain haploid. High degrees of polyploidy (4n-8n-16n) occur in muscle attachment cells in fourth and fifth instar drones and workers. Merriam and Ris (1954) concluded there is a positive relationship between the degree of polysomaty and the physiological activity of the cells in these bees.

C. Selection and Developmental Instability

Lerner (1959) stated, "The process of coadaptation is probably a continuous one, and under artificial selection, or, indeed in nature, it may happen that the selection pressure applied too strongly to some single traits outstrips the coadaptation process. The lag may be so great as to result in an unbalanced population which is in danger of extinction." Depending on the linkage relationships, strong selection for a specific trait may be so destructive to the genetic constitution of coadapted buffering systems that coadaptation may not always be restored after a single generation of outcrossing involving individuals from different highly selected lines. In a frequently cited paper Thoday (1958) may have given evidence of this situation. For 10 generations he selected for high and low lines of sternopleural chaetae numbers in *Drosophila melanogaster*. Selection was effective in producing gains, and in both the high and low lines there was an increase in fluctuating asymmetry. Each generation matings were made between members of the high and low lines, resulting in F_1 hybrids with intermediate numbers of sternopleural chaetae. However, and importantly, the F1 hybrids also manifested increased fluctuating asymmetry. Thoday proposed that strong selection for bristle number in both the high and low lines resulted in a deterioration of genic balance in complexes linked closely to those affecting bristle number, with the balance not being restored following hybridization. Since the hybrids are presumably more heterozygous than the individuals in the selected lines and do not manifest developmental homeostasis, these results are often cited by authors as evidence against Lerner's thesis that heterozygosity is uniquely responsible for developmental homeostasis, which, of course, was not his thesis. With developmental homeostasis also resulting from of interlocus interactions in homologous and non-homologous chromosomes, according to Lerner, strong selection for the trait could alter the allelic relationships in these chromosomes, as stated by Thoday, resulting in a disruption of buffering in the F_1 hybrids. Additional selection studies of this type are needed in *Drosophila melanogaster* and other species to

determine how often the results observed for sternopleural chaeta by Thoday occur for other traits.

D. Isozyme Polymorphisms

In his opposition to Dobzhansky's balance (overdominance) hypothesis, Crow (1987) emphasized that despite the great attention the problem has received and the statistical sophistication that has been used, there is still no convincing evidence that isozyme polymorphisms in natural populations are maintained by overdominance. He suggested that perhaps only a minority of these polymorphisms result from balancing selection. Fluctuating asymmetry, combined with isozyme technology, is a useful tool for testing for the presence of overdominance at a specific major locus, but its limitations must be taken into consideration. Overdominance at a locus could be detected at a locus by the tool of fluctuating asymmetry only if a stress is put on development by both enzymatic homozygotes. It would not be expected that polymorphism for *commonly occurring alleles* (A^1A^1, A^1A^2, and A^2A^2) at a major locus in a diploid species would be maintained by overdominance with both homozygotes manifesting developmental instability and increased fluctuating asymmetry. In the presence of alleles acting in this manner mutation pressure and natural selection would diminish developmental instability by substituting alleles with a less disruptive effect on development, or mollifying the effect of homozygosity for the alleles by modifiers. It is likely, therefore, that even if overdominance were present at a substantial number of major loci lending themselves to isozyme technology, most could not be detected by using the tool of fluctuating asymmetry.

In a widely cited series of publications, Leary et al. (1984, 1992), found that allozyme heterozygotes at various different loci in trout demonstrate more stability than the homozygotes, as demonstrated by increased fluctuating asymmetry in the homozygotes. The studies by Leary and his colleagues give strong support for the presence overdominance at the loci studied. However, the results are not easily interpreted because fishes of the family (Salmonidae) to which trout belongs have an ancient autotetraploid ancestor (Ohno 1970) and consequently have a number of isozyme loci coding for the same enzyme. Tetraploidy complicates the situation. Several questions can be asked. Did diverse subspecies contribute to the genomes of the ancestral tetraploid? How often did polyploidy

occur and was there mixing of gene pools at the polyploid level? Are the contrasted alleles in present trout populations suboptimal alleles that were favored by natural selection in antecedents of the ancestral tetraploid? Is the impact of natural selection lessened on the frequency of a suboptimal allele if multiple copies of the locus are present? Other isozyme studies showing evidence of increased fluctuating asymmetry in the presence of homozygosity have been criticized by Clarke (1993) as being only suggestive and not conclusive because of the history of the populations. Additional research of this type is needed in various different species, and especially diploid species.

CONCLUSIONS

The Crow-Muller model differs from Dobzhansky's and Lerner's model by stipulating that overdominance plays a minor role, if any, for developmental homeostasis. According to the Crow-Muller model, coadaptation is primarily a function of homozygosity for additive dominant alleles and the interlocus interactions of these alleles. Lerner's model specifies that coadaptation in Mendelian populations results from coadapted heterozygosity, coadapted homozygosity, and coadapted interactions among alleles at loci in homologous and non-homologous chromosomes. Although Lerner's model emphasizes the advantage of coadapted heterozygosity, it was his view that no Mendelian population can afford to have too many loci manifesting overdominance simultaneously. A special feature of Lerner's model is the presence in some Mendelian populations of complex highly heterozygous polygenic systems maintained by selection for the heterozygote with phenodeviants being segregants of these systems. Dobzhansky's model is similar to Lerner's model except for the additional assumption that heterozygosity for many genes and gene complexes may produce higher fitness even without prior coadaptation, and therefore generalized heterozygosity plays a role in the evolutionary process. Based upon all available information, there is no evidence to support Dobzhansky's views that overdominance occurs commonly at major loci in any Mendelian population. To date there is no evidence for or against Lerner's model that highly heterozygous polygenic systems exist in Mendelian populations because of heterozygote advantage. Polygenic loci, with the alleles involved in buffering do not lend themselves to easy analysis. Since, according to Lerner's model, phenodeviants are segregants of some of these polygenic systems, a test of his model is to look for candidate traits in various different

populations and to carry out the proper tests of hypothesis. Lerner's model can be discounted if phenodeviants, as defined by him, do not exist. Additional research is needed to determine how frequently overdominance occurs at major loci in various different species, and especially diploid species. If unequivocal evidence can be obtained for overdominance at a reasonable number of loci, and if phenodeviants can be identified, Lerner's model would be favored. At present there is no unequivocal evidence that rules against the Crow-Muller model.

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Key words

Canalization

Coadaptation

Coadapted gene complexes

Coadapted heterozygosity

Developmental homeostasis

Developmental instability

Developmental stability

Euheterosis

Fluctuating asymmetry

Genomic coadaptation

Heterosis

Heterozygosity *per se*

Internal coadaptation

Luxuriance

Overdominance

Phenodeviants

Relational coadaptation

Organisms Mentioned by Common Name or Taxonomic Name

*Apis mellifera (*Honeybee)

Iridomyronex humilis (Ant)

Drosophila melanogaster

Drosophila pseudoobscura

Poultry

Trout (Family: Salmonidae)