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Mid-Century Controversies in Population Genetics

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Annu. Rev. Genet. 2008. 42:1–16

First published online as a Review in Advance on July 24, 2008

The *Annual Review of Genetics* is online at genet.annualreviews.org

This article's doi: 10.1146/annurev.genet.42.110807.091612

0066-4197/08/1201-0001$20.00

Key Words

heterosis, genetic load, neutral theory, random drift, shifting-balance theory, classical vs balance hypothesis

Abstract

Beginning in the 1930s, evolution became an experimental subject. New techniques, especially in *Drosophila*, made possible quantitative analysis of natural populations. In addition to a large number of studies on many species, there were four major controversies that dominated much of the discussion and experimentation. Some of the arguments were quite heated. These controversies were: Wright vs Fisher on Wright's shifting-balance theory; dominance vs overdominance as an explanation of heterosis; the classical vs balance hypothesis for genetic variability; the neutral theory of molecular evolution. Curiously, most of these issues were not really resolved. Rather they were abandoned in favor of more tractable studies made possible by the new molecular methods.

A BIT OF HISTORY

After the publication of Darwin's *The Origin of Species* in 1859, the biological community almost immediately accepted the idea of evolution. In contrast, there was a great deal of reluctance to accept natural selection as a sufficient mechanism. Looking back, this seems surprising. For one thing, the idea of natural selection is remarkably simple and obvious; in fact many biologists must have thought, as did Thomas Huxley, why didn't I think of it? For another, the rediscovery in 1900 of Mendelism with its discrete hereditary units removed a major difficulty, the rapid decay of variance under blending inheritance (21). Nevertheless, although it is not possible to determine how numerous the doubters were, it is clear that a number of influential biologists did not accept natural selection, in several cases inventing other mechanisms (e.g., orthogenesis, nomogenesis), now largely of historical interest.

The turnaround came with the modern synthesis, as Julian Huxley (34) called it. A convenient starting point for this period is Fisher's pathbreaker, *The Genetical Theory of Natural Selection* (21). The book did not initially attract much favorable attention—mainly because it is very hard to read—but its subsequent influence has grown. To cite one example, Bill Hamilton in a cover blurb (21) calls it "a book that I rate only second in importance in evolutionary theory to Darwin's 'Origin.'" This period persisted for half a century, from 1930 to about 1980, by which time the wide application of molecular techniques changed the nature of the questions asked.

The modern synthesis brought about two major advances. It ushered in the "golden age" of population genetics, dominated by the three pioneers, Fisher, Haldane, and Wright. It also led to population genetics and microevolution becoming experimental subjects, led largely by Dobzhansky (19).

Immediately there was an explosive growth of experimental research in population genetics. A solid mathematical foundation had been laid by the three pioneers (10). There were early British attempts to measure the selective intensity in Lepidoptera. As early as 1924 Haldane took advantage of the rapid increase of melanotic forms of the peppered moth, *Bison betularia*, with increasing smoke pollution in industrialized Britain. The accumulated data give a rough idea of the time required for the change since this species conveniently has only one generation per year. Yet the uncertainties were great enough (e.g., initial frequency) to permit only a rough calculation [revised in (30)]. It was clear, however, that selection was intense, of the order of 50%.

Most important, however, was the introduction of *Drosophila* studies on evolution in natural populations. Sturtevant & Dobzhansky (58) showed how overlapping inversions, easily discernable (to the skilled) in the salivary gland chromosomes, could be used to infer phylogenetic sequences. The quantitative experimental study of natural populations began when Dobzhansky enlisted the help of Sewall Wright to guide and analyze his studies of natural populations of *Drosophila pseudoobscura* and its relatives. This marked the first attempt to measure the parameters that appear in Wright's theory. The methodology combined standard *Drosophila* analytical techniques, such as use of marker chromosomes containing crossover-suppressing inversions, with data from natural populations. Dobzhansky had ushered in a whole era of population genetics of natural populations. And it exploded. Dobzhansky and his group wrote one paper after another, and starting in 1938 these were numbered [these publications are reprinted in (44)]. I refer to them by number. The Wright-Dobzhansky paper is number V.

Originally, Sturtevant and Dobzhansky had planned a systematic study of *Drosophila* populations. For reasons that seem to be largely personal (51), Dobzhansky continued alone. Interestingly, one of the first conclusions of the Wright and Dobzhansky paper (44, number V), namely that recessive lethals in natural populations were too infrequent to be consistent with mutation-selection balance

in a large population, was first noted by Sturtevant.

I discussed the mathematical developments of this period in an essay some two decades ago (10). In this article I propose to emphasize the experimental approach that characterized the period. One characteristic of the time was a search for generality, both theoretically and experimentally. Although the experiments were necessarily particular, the object was to arrive at a general conclusion. Such a search almost inevitably led to differences of opinion, often to serious controversy, and sometimes to personal acrimony. These became a major feature of population genetics at the time.

Although there were countless experimental studies, it seems to me that the period is best characterized by a few attention-getting controversies. I have therefore decided to structure this review around four major controversies of the period. I'll include some personal history, since I was involved in each of these, sometimes from near center, in others from closer to the periphery.

WRIGHT VS FISHER: THE SHIFTING BALANCE THEORY

The shifting balance theory was strictly a one-man show. The idea came to Wright in the 1920s and although he wrote one paper after another, these were all authored by him alone. His first major paper was in 1931 (67). Furthermore, although the papers were updated and the mathematics improved or the emphasis changed for different audiences, the message remained essentially the same. Wright was not only the inventor, he was the principal protagonist. His last paper (70), written only weeks before his death, reiterated the same theme, much as he had expressed it half a century earlier. It is remarkable that a single idea, formulated and promulgated by a single person, has had such a large and lasting influence.

Another attribute of the theory is that, as usual with Wright's work, the ideas grew out of his own observations. The theory depends heavily on his studies on inbreeding and gene interaction in guinea pigs and his analysis of the history of shorthorn cattle. Inbreeding showed differentiation between the guinea pig lines, and Wright was repeatedly impressed by unexpected phenotypes when coat color genes were combined. The cattle history led him to conclude that improvement came not so much from mass selection as from differences, seemingly random, among herds. Exporting bulls from the best herds upgraded the whole breed, and the process could then be repeated.

To Wright, the major problem with natural selection was how to evolve complex interactions, the totality of which is beneficial whereas individual components are not. How can a population go from a state with one set of coadapted genes to another, perhaps a better one, if the intermediates are poorly adapted? This cannot happen by mass selection in a large population, except for such unlikely events as fortuitously linked loci. Wright's solution was a large population, with many partially isolated subpopulations. One of the subpopulations might happen to drift into a good gene combination, in which case it would grow disproportionately and export migrants to surrounding subpopulations, eventually spreading through the whole population (68). This view was extremely popular with biologists. Most important for the success of the theory, Dobzhansky was particularly impressed and popularized Wright's work in his influential *Genetics and the Origin of Species* (19). Likewise Wright's view was adopted by Simpson in his book *Tempo and Mode in Evolution* (55), which brought Wright's work to the attention of paleontologists. Wright's theory with his adaptive peaks and valleys metaphor came to be standard vocabulary, cited everywhere in writings on evolution and genetics.

The theory had its critics, especially among the more quantitative thinkers. They pointed out that the process required a subdivided population with a rather delicate balance among subpopulation sizes and migration rates. Furthermore, when subpopulation size, migration, and selection are optimal for the theory the population fitness is low (11); a theory in which the major process occurs during a period of

Shifting-balance theory: Wright's hypothesis that a structured population with migration and random drift is optimal for evolutionary advance

fitness reduction was not inviting to many. Of course, Wright knew this, but he did not regard it as a serious flaw. He persisted in using his basic metaphor of peaks, valleys, and ridges.

However, as Fisher said, given a perpetually changing environment, Wright's fitness surface might better be characterized by undulating ocean waves rather than a rugged landscape. Then, such evolutionary hang-ups may not occur, or would not be a serious deterrent. Fisher argued that hardly ever would a population find itself in such a situation that no allele frequency change could increase fitness. Rather than consider a particular phenotypic change, as Wright did, Fisher argued for any change that would improve fitness. The theory is predictive in terms of increased fitness, but it doesn't predict elephants or fungi. But neither does Wright's theory.

Fisher argued that a large population is advantageous because it has a larger supply of mutant genes and also because chance effects are minimized. His great triumph was to show that natural selection acts on the additive component of genetic variance, as defined by least squares. [See the 1999 revision (21).] Nature had anticipated Gauss. Fisher showed that dominance variance does not contribute to parent-progeny correlation and argued that epistatic variance would probably be unimportant; he thought that efforts to subdivide epistatic variance, a popular subject in the 1950s, were a waste of time. The nonimportance of epistatic components was finally shown by Kimura (17, p. 196 ff; 36), but alas only after Fisher's death. Kimura showed that (unless linkage is very tight) a population under directional selection soon creates just enough linkage disequilibrium to cancel the epistatic variance. Therefore, taking epistasis into account will often make selection predictions worse rather than better.

The differences between Fisher and Wright were exacerbated by the fact that they didn't like each other. Fisher often seized an opportunity to criticize Wright. This was not unusual, for Fisher was outspoken and often made enemies. He seemed to enjoy insulting people. Wright was different. He was the gentlest of men and rarely said anything bad about anyone. Wright's theory gradually lost popularity in the later years of the century. The criticisms became more forceful (5, 6). The theory was kept alive largely by Wright himself, who continued to advocate it well into his nineties. He had a few staunch defenders (26, 64). Wright's last paper, published in the year of his death, was a spirited defense of his peaks and valleys model (70). Provine (52) had criticized Wright for changing the definition of his abscissas in his fitness surface, where fitness was the ordinate. Wright replied that this was intended as a metaphor, not as a geometrical construct. Wright's article also included a more sympathetic account than previously of the ideas of Fisher, Haldane, and Kimura. But he still thought that his shifting-balance theory should play a major role in evolutionary theory. Since Wright's death in 1988, one hears much less. His theory has lost its strongest advocate.

One possible reason for its declining popularity is that the question is not such that it could be settled by key experiments. Although there were some experiments that supported some aspects of Wright's theory, Wright himself never thought that they answered the big question. For him, rather than being capable of settlement by experiment, it was a matter of indirect evidence and logic. This is an extreme example of the search for breadth and generality, in this case so broad as to defy testing.

Although the shifting balance theory may not last, some of the questions that it raised are a permanent part of population genetics. Wright's name is insured a place in genetics history for the inbreeding coefficient, effective population number, and F statistics. Who wouldn't be proud of such a simple, elegant way of measuring the effects of inbreeding, relationship, and population structure?

One of Wright's most useful devices is the concept of effective population number. This is the size of an idealized population (e.g., randomly mating with each parent having the same expected number of progeny) that has the properties of the actual population under study. I

made a contribution to the field by noting that there are several ways of defining effective population number of which two are most important: (*i*) the inbreeding effective number, the size of an idealized population (binomial or Poisson progeny distribution) with the same change in heterozygosity as the observed population: (*ii*) variance effective number, the size of an idealized population with same amount of random gene-frequency drift as the observed population (9). The reason Wright missed this distinction is that in each of the cases he considered they were the same. I also developed ways of estimating these from demographic data (15). This work has been carried much farther by others and is now part of standard population genetics theory (66).

Wright's F statistics are also here to stay. F_{ST} in particular is widely used as a measure of population substructure, independent of allele frequencies (14). Wright realized the great strength of directional migration, which subsequent study has confirmed (16).

In addition to writing theoretical articles, Wright spent an enormous amount of time on data analysis. Although he often wrote about the shifting-balance theory, this was not how he spent most of his time. After retiring from the University of Chicago at age 65 to accept an appointment at the University of Wisconsin, he spent several years analyzing his guinea pig data. He then started on his four-volume magnum opus, published between 1968 and 1978 (69). This is a review of his own work, mathematical and experimental. But even more of the book is devoted to the work of others. Almost always Wright's review involved a reanalysis of the data, usually with extensive calculations. The most extensive example (69, Vol. 4) is his enormously detailed analysis of the data of Epling and Dobzhansky on the tiny desert plant, desert snow (*Linanthus parryae*). This illustrates abundantly Wright's characteristic meticulous attention to detail and his zeal for quantitative analysis, usually using his own methods, to make sense out of an enormous amount of heterogeneous data. Another example is his analysis of color patterns in the snail, *Cepaea nemoralis*. Here as usual he emphasized the effects of random drift. As often happened, geneticists of the Fisher school argued for selection, in this case the major effect was attributed to bird predation (3).

Ironically, although Wright's name will remain a part of population genetics and evolution, it will likely not be for the work that he regarded as most important.

HETEROSIS: DOMINANCE VERSUS OVERDOMINANCE

Overdominance: the state when the heterozygote exceeds the performance of either of the two constituent homozygotes

Heterosis: increased vigor and performance of hybrids

One of the greatest economic contributions of genetics, if not *the* greatest, has been the development of hybrid maize. Typically, the hybrid between two inbred lines exceeds the performance of the randomly mating populations from which the inbred lines were derived. From the earliest days, in the 1910s and 1920s there have been two hypotheses (8): the overdominance hypothesis, that the increased performance is mainly due to loci at which the heterozygote performs better than either homozygote, and the dominance hypothesis, that in the hybrid deleterious recessive alleles brought in by one parent are concealed by dominant alleles from the other. In the very earliest days, the overdominance hypothesis prevailed (53) but was soon displaced by the dominance hypothesis, which persisted as the favored mechanism into the 1930s and 1940s. The first compelling argument came from D. F. Jones, who pointed out that multiple loci with linkage could account for heterosis without invoking overdominance (35).

In the 1940s, Fred Hull resurrected the overdominance hypothesis (33). One of his arguments was the failure to achieve significant improvement by mass selection or by selecting within inbred lines. A second argument came from constant parent regression. The regression of F_1 on one inbred parent, with the other parent held constant, has different expectations with dominance and overdominance. With overdominance the regression may be negative when the constant parent is high-yielding. Hull found evidence for such a

regression. At about the same time, Comstock and Robinson in maize and Dickerson in swine produced arguments for overdominance. In 1950 there was a month-long summer heterosis conference at Iowa State College in which their arguments were presented (27).

At this conference, I repeated an argument first published in 1948 (7), arguing for the insufficiency of the dominance hypothesis. This was based on the Haldane mutation load concept (29), (which I had rediscovered, thinking I was original). Treating yield as fitness, the reduced yield from recessive mutations equals the haploid mutation rate, which I took to be 0.05. If all recessive mutations were replaced by dominant alleles, the increased yield would be about 5%. Yet, the observed values were often 10 or 15%. I regarded this as evidence for overdominance. In retrospect, I think it is a rather weak argument. I was pleased, however, to have it accepted by Fisher (22) in his Appendix C.

Nevertheless, this, along with arguments of a different sort from Comstock and Robinson in maize and Dickerson in swine, carried the day at the heterosis conference. Overdominance was in the air. Several breeders, both animal and plant, planned selection programs designed to capitalize on overdominance. Particularly popular was reciprocal recurrent selection, designed to utilize both dominance and overdominance (4). A number of experiments designed to test this system over the next few years usually gave equivocal results.

Although I argued for overdominance in explaining hybrid excess yield, this did not imply a similar causation for inbreeding decline. With an overdominant locus, an increase or a decrease in heterozygosity would have roughly symmetrical effects. In contrast, with dominance, making an equilibrium population more heterozygous would cause only a slight increase whereas making it more homozygous would cause a large decrease. I summarized my view this way (8):

> I should like to suggest the following interpretation of the effects of inbreeding and hybridization: The deleterious effects of inbreeding and the recovery on hybridization are mainly due to loci where the dominant is favorable and the recessive allele so rare as to be of negligible importance in a noninbred population. Variance of a noninbred population, and hybrid vigor when measured as in increase over an equilibrium population, are determined largely by genes of intermediate frequency, probably mostly overdominants.

Within a very short time after the Heterosis volume, two additional facts became apparent. One was the realization that complete recessiveness is rare and slight partial dominance is the rule. Since most such mutations are then eliminated as heterozygotes, the mutation load is doubled and so is my limit for yield increase from removal of performance-reducing recessives. Also, newer *Drosophila* data argued that mutation rates were probably higher than I had assumed. So the force of my argument was much diminished. In 1956 Sprague published the results of a maize experiment that made clearly different predictions from the two hypotheses. Two populations were selected for improved performance in hybrids with an inbred tester. With overdominance, the two strains would tend to accumulate genes complementary to those of the tester but similar to each other. This would lead to decreased yields in the two strains and in crosses between them. With partial or complete dominance, in contrast, each of the populations would show increased yield, and so should the hybrids between them. This is what was found. Sprague presented preliminary results at an international congress in Tokyo in 1956 (56) and this added greatly to my doubts, which were already developing.

Meanwhile, the experiments of Comstock and Robinson had been carried more generations and, after greater opportunity for recombination in later generations, what had appeared to be overdominance turned out to be the result of repulsion linkages (13). At the same time experiments to measure additive variance were finding considerable amounts. For several years, mass selection had become much more

effective. There were two reasons: (*i*) better control of the parentage in field experiments, and (*ii*) better experimental design as Fisher's methods became widely adopted. Finally, there was substantial improvement in inbred lines, so that they were comparable to the best hybrids of only a few generations earlier.

There is now solid evidence, especially in maize, that the great bulk of the genetic variance is additive with dominance. There is a measurable, but small effect of epistasis. but little or no detectable contribution from overdominance, at least in maize. I suspect that the best hybrids may get an additional boost from overdominance or epistasis (13). We can expect clarification from QTL mapping. As expected, some of the earlier results suggesting overdominance have been resolved into two or more tightly linked, partially dominant loci.

In contrast to the Wright-Fisher arguments, there were no strong personal disagreements, certainly no strong antagonisms. Why? I think the reasons lie in the personalities of the people involved. Early advocates of overdominance, Hull, Comstock, Robinson, and Dickerson, were more impressed by experiments and less inclined to arguments. Likewise, Sprague who provided the strongest evidence for dominance was never argumentative. And as one participant, I managed to have friendly relations with both schools. The issue was potentially as divisive as shifting balance, but the differences never became personal.

POPULATION STRUCTURE: THE CLASSICAL VERSUS THE BALANCE HYPOTHESIS

Just as the shifting-balance theory was the creation of one man, the balance hypothesis was also, in this case Theodosius Dobzhansky. He introduced it at the 1955 Cold Spring Harbor Symposium on Quantitative Biology, at which he gave the keynote address (20).

Dobzhansky had been and still was a most influential figure, and deservedly so. As I said earlier, he had the largest hand in making evolution and population genetics experimental subjects. Together with Sturtevant, he had inaugurated a series of studies of natural *Drosophila* populations. He did experiments to measure Wright's parameters. And he had done more than anyone else to popularize and clarify Wright's views.

At the time the prevailing view of population structure was that at most loci there was a single favored allele, usually dominant or partially so. Heterozygosity was due to recurrent mutation, migrants, favorable alleles in the process of fixation, or alleles close to neutrality. The contribution of these was thought to be small. There was also a contribution from balanced selection, either selection favoring rare alleles or overdominance. The contribution of balancing selection to the population variance could be large, but the proportion of loci affected could still be small, since each locus maintained by balancing selection contributes much more to the variance than classical loci maintained by recurrent mutation (8).

Dobzhansky's eye-opener was the argument that, *at the individual gene level*, heterozygotes are more fit than homozygotes. He did not arrive at this unorthodox view lightly. Although long interested in heterosis, he had thought it was the result of intrapopulation selection, presumably for coadapted genotypes. This view was contradicted by the findings of Vetukhiv (63), who found heterosis in hybrids between populations. This, to Dobzhansky, implied that heterozygotes were intrinsically more fit. He had been strongly committed to intrapopulation selection for coadaptation. Nevertheless, the data were compelling, so he reluctantly concluded that intralocus heterozygosity was favorable for fitness. Once convinced, he became a determined advocate.

One might think that this is essentially the same as the dominance-overdominance hypotheses for heterosis. But there is an important difference. In the dominance-overdominance argument the issue was the amount of genetic and phenotypic variance attributable to the two mechanisms. It was known that a small number of overdominant loci can contribute disproportionately to the population variance, so there was no assumption that a large fraction of

Balance hypothesis: the typical locus is overdominant at the gene level; thus most loci are heterozygous

Classical hypothesis: at most loci there is a normal allele, usually dominant, and the variability is due to new mutations, transient polymorphisms, migrants, and such. In particular balanced polymorphism is not a major component

individual loci were overdominant. Dobzhansky, in contrast, believed the majority of individual loci were in fact overdominant.

Dobzhansky did not shun controversy and in this case his principal antagonist was H. J. Muller. Muller's views were largely those prevailing at the time. He was totally unconvinced of Dobzhansky's overdominance theory. Although more genetic variability would be expected under the balance hypothesis, this was not the main issue. Genetic variability was simply there, whatever the amount; the important question was not its existence, but its cause.

How could ubiquitous overdominance be tested? The most direct way would be to compare the effect of new mutations in homozygous and heterozygous background. Since the effects were sure to be small, this would have to be a heroic experiment involving millions of flies. The hero in this case was Bruce Wallace (65). In these experiments, one set of chromosomes had been exposed to 500 r of X rays. The matings, involving *Cy L* and *Pm* chromosomes (Curly wings, Lobed eyes, and Plum eye color), were contrived to yield four classes of progeny. The + chromosomes had already been rendered essentially isogenic. Here are the crucial genotypes. The numbers are viability, relative to the *Cy L/Pm* class. The underlined boldface chromosomes had received radiation.

Control	*Cy L/Pm*	*Cy L/+*	*Pm/+*	+/+
	1.000	1.094	1.146	1.008
X-rayed	*Cy L/Pm*	*Cy L/±*	*Pm/+*	+/±
	1.000	1.115	1.137	1.033
Ratio	1.000	1.019	0.992	1.025
Probability		<.05	>.30	<.01

The +/+ vs +/± comparison argues that the heterozygous effect of radiation enhanced the otherwise homozygous viability by 2.5%, in agreement with Dobzhansky's expectations. Wallace concluded that at least 50% of the loci in a natural population were heterozygous.

This result was very hard for Muller and a number of others (including me) to accept. Yet it was also hard to fault Wallace's experimental technique. As described in (65), the experiments were very carefully designed and any obvious sources of bias were ruled out. It was puzzling, however, that the *Cy L/+* comparison was also significant, although at a lesser significance level. Could this mean that radiation was beneficial irrespective of whether the chromosomes were otherwise homozygous or heterozygous? This seemed even more unlikely.

What might have been a purely scientific controversy was rendered political by the debates going on at the time about the development and testing of nuclear weapons. Muller had argued forcefully that any amount of radiation, however small, does a proportional amount of damage and this view prevailed in the National Academy of Sciences report (1). But those interested in the development of nuclear energy were eager for any evidence that radiation was less harmful, so Wallace's results were very popular in these circles, whereas Muller was *persona non grata*.

Wallace's results remained to be understood. Those who were reluctant to believe them attributed the results to undetected biases. Furthermore, the effect expected was so small that it might well be obscured by extrabinomial noise in the system. The controversy remained.

I finally decided that it was important to repeat the Wallace experiments, but to devise a way to require fewer flies to count. These experiments utilized two conspicuous eye colors, cinnabar and brown. Having only two classes of flies simplified the counting and would be expected to reduce errors. The second major modification was to carry out two radiation experiments simultaneously, such that each was a control for the other. Experimental and analytical procedures are given by Maruyama & Crow (45). With this arrangement, each fly contributed four times as much information as with the Wallace technique, plus time saved by having to classify the flies into only two conspicuous classes instead of four.

The results again confirmed Wallace's. Flies carrying an irradiated chromosome that was otherwise identical to its partner showed a viability increase of about 1.5%. The amount of radiation was 1000 r, enough to produce about 0.2% decreased viability from heterozygous

effects of lethals, so the seeming increase in viability was considerably more than enough to offset the known effect of induced lethal heterozygotes.

One more experiment was done, this time by Pandey (50). Except for a number of intervening generations of inbreeding, this was a repetition of the Maruyama and Crow experiments. This time the data were inconclusive, although when added to the earlier Maruyama experiments the net effect was to support Wallace (46). Could it possibly mean that radiation has some previously unsuspected effects? The prevailing opinion, however, was that the signal to noise ratio was too small.

The response to Wallace's work is curious. Empiricism and data did not seem to carry much weight for most geneticists. The BEAR Report (1) came before Wallace's papers. It followed the classical view. Although there were deep divisions in the committee, they were on other grounds (12). Later BEAR reports and those from many other policy-making groups continued as if the Wallace work did not exist. The Maruyama paper was too late to have any significant influence. Many geneticists simply ignored these results. The usual explanation was that the effect being sought was so small that it was likely to be obscured by the noise of uncontrolled environmental variables. One reason for this being ignored by various committees was that if Wallace were correct, more than half the loci would be heterozygous. On his hypothesis new mutations at these loci would be deleterious; hence the overall effect of radiation would be harmful. So for real populations, even if the Wallace view were correct, his controversial findings had little relevance. However, I do not recall this argument being used.

Dobzhansky continued to do experiments purporting to show overdominance (44, XXXII, XXXIV, XXXVI, XXXVII, XL). None of these stood up to criticisms. Likewise, results from other labs, including mine, did not really demonstrate the absence of ubiquitous overdominance for fitness, although they made it very unlikely for viability alone.

The first attempt to use Haldane's genetic load theory for this problem (29) was by Morton, Crow, and Muller (47). Data on the excess mortality from consanguineous marriages permitted an estimate of the number of lethal equivalents per gamete. (A lethal equivalent was defined as a group of mutant genes of such number that, if dispersed in separate individuals, they would cause on the average one death, e.g., one lethal mutant, two with 50% probability of death, etc.) The number, mostly hidden in heterozygotes, was estimated at 3–5 per zygote. *Drosophila* data had shown that newly arisen lethal mutations reduce heterozygous viability by about 5%; lethal mutations extracted from nature have a lesser effect, of course, and the estimated value was 2%–3%. Later, direct measurement of fitness in natural populations of several *Drosophila* species were in substantial agreement (18). Using this, the number of expressed lethal equivalents could be computed. Then the assumption of mutation-selection equilibrium permitted a calculation of the mutation rate. This was estimated as 0.03–0.05 per generation, for the class of viability mutations detected in the consanguinity studies. Needless to say, the numbers were extremely uncertain, but the study pointed the way to a better understanding of mutation-selection balance. The authors argued that, unless the allele number is large, overdominance is not likely to make a substantial contribution to the inbred load.

Lethal equivalent: a group of genes that when dispersed in separate individuals leads to one death; i.e., one lethal gene, two with 50% probability of death, etc.

This is a good chance for me to correct an error in my earlier thinking. I did not distinguish between the number of generations a deleterious mutant allele persists before elimination and the number of individuals carrying that mutation during this time. In retrospect it is obvious that the latter must be larger, since there must be at least one each surviving generation. This error was belatedly rectified, taking stochastic processes into account in (24).

The Morton et al. study (47) could measure only lethal equivalents and offered no evidence on whether the effect is from a few lethals or a larger number of minor mutations. We used the second chromosome of *Drosophila*, with its

markers and crossover suppressors, to make this distinction. The analysis used genetic load theory and took advantage of the fact that the distribution of homozygous viability effects was strongly bimodal. There were a number of mutations that were lethal or nearly so. Then there was a much larger number with very small effects on viability and that graded imperceptibly into normal. They could be measured only statistically (28). The fact that there were very few mutations with intermediate viability permitted a separation of the two groups. The experimental data showed that the load from mildly detrimental mutations was about 60% as great as for lethals (28). The clear implication is that minor mutations have much greater dominance than lethals, enough that the heterozygous elimination rates are comparable. Clearly, there is no room for much overdominance.

These studies all assumed that mutations were largely independent in their effects on viability. Although they had substantial dominance, especially the minor mutations, the studies of single chromosomes gave no information about possible epistatic effects. This was studied by measuring simultaneous homozygosity for mild mutations on the second and third chromosomes. Lethals were by definition independent; there were, however, a few synthetic lethals. The results showed that epistasis was small; the viability of a double mutation was about 2% less than if the two chromosomes had independent viability effects (62). Dobzhansky found a somewhat larger effect (44, XXXVI). Intrachromosome comparisons were made by using two levels of inbreeding. Again the results showed real, but slight synergistic epistasis (62).

The picture that emerged from inbreeding studies in *D. melanogaster* is one of relative simplicity. Dominance is large enough that most elimination of mutations is through heterozygous effects, and is much greater for mild than for drastic alleles. In fact, the data suggest that as the mean effect approaches zero the heterozygote approaches exact intermediacy between the two component homozygotes. There is relatively little epistasis.

These studies all concerned viability. We also did a study of fitness effects of EMS(ethylmethane sufonate)-mutagenized chromosomes. By using a translocation between the X and second chromosome, the system was contrived so that the males remain heterozygous generation after generation, thus permitting fitness measurement. The most striking effect was that the effect of a mutation on total fitness was much larger than viability effects alone (54). But again, most selection against deleterious recessives is through their heterozygous effects. There was no support for the balance hypothesis. Yet there was not a definitive answer to the question of the source of population variability. Clearly, mutation contributed a substantial amount, but the importance of other mechanisms remained uncertain.

Dobzhansky continued to argue for ubiquitous overdominance. He died in 1975 and until shortly before his death he "devoted a large part of his remaining scientific work to an unsuccessful attempt to demonstrate the generally superior fitness of genic heterozygotes (42)."

My own relations with Dobzhansky were uneven. At the Iowa heterosis conference he was extravagant in his praise of my work on heterosis, which agreed with his ideas. Then with the classical-balance argument, he and I found ourselves on opposite sides and this soured his relationship toward me. I found, as others had, that it was almost impossible to have a scientific difference with Dobzhansky that did not become personal. Later I found a way of reconciling our differences, so toward the end of his life, we were on good terms. In contrast, despite deep differences in scientific views, Bruce Wallace and I remained on friendly terms.

In the 1960s the technique of gel electrophoresis became popular. Early results (43) showed a level of genic heterozygosity that, when corrected for undetected variability, could be 25% or more. This was more than classicists would have expected. This finding immediately stimulated an orgy of electrophoretic studies in hundreds of species. Nevo (49) summarized 968 studies from 17 major taxa including 968

species. The average amount of heterozygosity was 0.054 for vertebrates, 0.100 for invertebrates, and 0.075 for plants, not as much as the early studies (43) suggested, but a substantial amount nevertheless. It was consistent with either the classical or the balance model.

Although these studies provided abundant data on the amount of variability, they did not offer any insight as to what the causes were. According to Lewontin (42), the source of genetic variability in populations "remains, today, the outstanding experimental problem of population genetics, since on its solution depends the correct evolutionary interpretation of the vast genic polymorphism now known to exist in virtually all organisms."

The question was not resolved to everyone's satisfaction. The arguments were not settled; they were simply dropped. The main reason for this was the coming of Kimura's neutral theory. There was a new bandwagon. The major emphasis shifted from the interpretation of genetic variability to evolutionary change.

THE NEUTRAL THEORY OF MOLECULAR EVOLUTION

The neutral theory had forerunners in bacterial genetics. Ernst Freese (23) invoked neutral mutation pressure to explain the fact that different bacterial species differed greatly in DNA base composition, despite similarities in amino acid composition. A similar argument was made by Sueoka (59). Neither of these had any great influence, perhaps because most students of evolution were interested in multicellular organisms.

The theory became a controversial issue with the publication of two papers. Kimura (39) was impressed by the great rate of molecular change implied by recent studies of molecular evolution. The rates seemed too rapid to be consistent with Haldane's (31) cost of selection. So he concluded that the changes were neutral and driven by mutation. This could be criticized by Kimura's inclusion of total DNA rather than only coding regions and by the limitations of the Haldane theory, especially with truncation selection. The paper by King & Jukes (41) was more chemical. They noted that the frequency of amino acids in vertebrates is roughly predicted by base frequencies and the code. Further evidence came from the synonymy in the code.

Neutral theory: the hypothesis that most evolution at the molecular level is driven by mutation and random drift, rather than selection

Kimura noted, as others did, that for neutral mutations, defined as having a selective difference small relative the reciprocal of the effective population number, the rate per generation of evolutionary substitution of new mutations is equal to the individual mutation rate per locus per generation. This depends on the period of observation being long relative to the time required for an individual substitution. The answer came soon. The mean conditional time for fixation of a neutral mutation is 4N generations, where N is the effective population number (40). Fortunately, most molecular studies involved longer periods. This immediately offered an explanation for a remarkably constant molecular clock, previously noted by Zuckerkandl & Pauling (71), but without an obvious mechanism.

The opposition was immediate and vociferous. To most evolutionists, natural selection was *the* mechanism. Any trait that could be observed would have a selective value greater than the reciprocal of the population number. The only exceptions would be highly inbred strains or small populations, such as might result from a bottleneck. To some extent the early arguments were at cross purposes. Classical evolutionists were thinking mainly of observable traits; the neutralists were concerned with DNA changes.

At first King and Jukes were involved in the controversy, but after a short time the argument was carried on almost entirely by Kimura, sometimes with his associate Tomoko Ohta. In rapid succession, Kimura added to his arguments. Any new finding provided another possibility for further evidence. Kimura was fortunate in another regard: he owned a set of mathematical tricks that were particularly well suited to this controversy. While still a graduate student at the University of Wisconsin, he had worked on a number of basic problems in population genetics and these proved to be very

useful for the neutral theory. He was especially inventive in using diffusion equations; in particular, he pioneered in the use of the Kolmogorov backward equation. Rather than references to individual papers, I'll refer instead to a collection of his most important contributions (39). [For a nontechnical account of the neutral theory, see (38).]

The rough constancy of protein evolution rates in different groups was among the strongest early evidence. Different proteins differed greatly, presumably because of different frequencies of amino acids that were selectively constrained, that is, sites at which mutations were unfavorable and eliminated by natural selection. But within a protein, the rates were roughly constant over wide phylogenetic differences. Additional evidence came from the fact that the least essential proteins or parts of proteins evolved most rapidly. One of Kimura's favorite examples was insulin, in which the discarded part of the molecule evolved most rapidly (38). Further evidence came from the greater rate of change for less disruptive changes in the molecule. As more and more evidence from the DNA code appeared, synonymous changes were found to be more rapid than nonsynonymous. Regions of DNA outside the coding region evolved rapidly, as did pseudogenes.

This evidence was not convincing to everyone. In particular, the evolutionary rates were not really constant, but were often quite variable. Kimura's view was that, since there are many reasons why the process would not work perfectly, the near-constancy was more important than the relatively small departures therefrom. For others the fluctuations were too large to ignore. The most telling opposing arguments came from mathematicians Gillespie and Matsuda (25, 61). They pointed out that fluctuating selection coefficients could effectively mimic the neutral data. They regarded such variations of selection coefficients as biologically more likely than strict neutrality. Later, Takahata (60), by this time having changed allegiance from Matsuda to Kimura, pointed out a number of ways in which rate irregularities were consistent with the neutral theory.

And so matters stood. Over the next decade the debate subsided. Although several people thought that Gillespie had an equally strong, if not stronger, argument, nevertheless the neutral theory largely prevailed. I think the major reason is its simplicity. That the rate of evolution is simply the mutation rate is very appealing, compared to the difficult mathematics of Gillespie and Matsuda. At the same time the neutral theory has been widely adopted for practical reasons. It is the natural null hypothesis for studies of selection and is increasingly used for this purpose. And, as already mentioned, it gives a simple, realistic explanation for a molecular clock.

It is doubtful whether the neutral theory is as important and widespread as Kimura thought. Yet, for noncoding DNA, synonymous changes, and such there is reason to expect neutrality. I think a reasonable summary is that most of the DNA in vertebrates is evolving neutrally. In contrast, the amount of neutrality for proteins is more in doubt. In recent years, more and more examples of positive selection have been demonstrated. The answers are coming from case-by-case studies.

The neutral theory is much like the shifting-balance theory. Both are largely the work of one person [if we ignore the early contribution of King and Jukes (41)]. The major advocacy and major arguments came from one person. But there is one difference. Wright was a strong adherent of his view and he repeatedly stated it. Yet he never was resentful of criticisms, at least in the later years after Fisher's death in 1962.

In contrast, Kimura was an active, indeed belligerent, protagonist for the neutral theory. Opponents of his view often became personal enemies. [For an amusing, witty account of the personal argument between Kimura and Gillespie, see (2).] Defending the theory and finding new evidence became a major obsession for the rest of Kimura's life. Why was the argument so heated? I think the reason, as with the shifting-balance theory and classical vs

balanced hypothesis, lies in the personalities of the people involved.

CONCLUSION

There were, or course, other controversies in population genetics during this period, although I think these four were the major ones. Here are two other examples. One was controversy as to the polygenic mutation rate, based on mutation-accumulation studies in *Drosophila* (48). Different laboratories reported widely different results. But these all involved the difficulties of measuring the magnitude of a familiar quantity, the mutation rate, rather than an important concept. The other was the idea of punctuated equilibrium, introduced by Gould and Eldredge. But this is an issue of long-time evolution, not population genetics.

An issue that is emerging as a controversy is that between the evo-devo (evolution of development) group and population geneticists. Although the approaches are different, both are trying better to understand evolution. Nevertheless there are the beginnings of a controversy. An opening salvo was fired by Hoekstra & Coyne (32). Whether this develops into a major controversy remains to be seen. One fact that argues against this is that newer molecular techniques yield results so quickly that there may well be a resolution before a controversy has time to develop.

One reason for the twentieth-century controversies that I have discussed is that, judged by current standards, the techniques were very limited. An investigator did an enormous amount of work to obtain a single result, and often this was inconclusive. With important questions that remained unanswered for a long time, it is not surprising that different viewpoints emerged. And the questions studied were indeed important ones, ideas that people took seriously and felt strongly about.

I don't intend to imply that most of the work in population genetics during this period involved these controversies. This was a period when the field grew and publications increased rapidly. This growth led to a new journal, *Evolution*. There were numerous studies of inbreeding and crossbreeding, selection in many species, mutation, isolating mechanisms, and speciation. At the same time there were many studies of natural populations, many stimulated by the then-new electrophoretic techniques. Plant studies also surged, with many species analyzed (57). A good source of information on the variety of such studies is Wright's four-volume compendium (69).

The dominance-overdominance controversy never became bitter. For the other three, it did. Did the bitterness of the controversies advance the science? Some thought so. The science historian Will Provine (2) took delight in the neutral controversy: "It's the greatest topic in the world. I can't even begin to tell you how much fun it is. People just fight like crazy."

My own opinion is that the controversies did not advance the field; they may even have retarded it, by keeping protagonists from working cooperatively and perhaps gaining deeper insights. I would like to have seen Kimura and Gillespie put their heads together. To my taste, the heterosis noncontroversy is closer to the way I would like to see science operate.

At the same time, although personalities may be the reason for the acrimony, there is a better reason why the controversy persisted: The questions were simply not answerable with the techniques of the time.

In the early days of the new synthesis, evolutionary problems dominated the thinking of many, perhaps most geneticists. Studies of developmental genetics received less attention. But in the 1940s progress in basic genetics advanced very rapidly; from biochemical genetics of Neurospora, sexuality in bacteria and viruses, and eventually the DNA model. The questions that seemed so important a few years earlier were for the most part not answered. They were simply dropped in favor of other questions that were more promising. Some are being or will be answered by molecular techniques. And the answers that once were so elusive will be obtained, likely not in a general way, but on a case-by-case basis.

ENVOI

It is hard to contemplate this period, with its dominating controversies, without pangs of sadness. In those days, people did an enormous amount of work to obtain minimal, often equivocal results. The experiments of Wallace (65) and Mukai (48) involved counting millions of *Drosophilas*. Now we think nothing of databases including tens of thousands of genes and hundreds of thousands of variants. But the machines do the counting. How different life for these people would have been if they had had only a few of the tools that are now available. At the same time, the experiments were often very clever, e.g., *Drosophila* techniques that involve crossover-suppressing inversions, to complement the happy circumstance of absence of crossovers in males. Thus for the first time whole chromosomes could be analyzed, a major technical triumph greatly increasing the resolving power. Haldane's genetic load theory (29) opened up new areas. And finally, we must marvel at Kimura working his magic with diffusion equations. I hope that with the power of computers, we don't forget the great insights gained by deep thinking.

My major regret is that the subject of origins of genetic variability and the selective mechanisms operating on these have been largely dropped. We still don't know how important balanced polymorphisms are relative to mutation selection balance and other selective mechanisms. It is still a burning issue in population genetics. When the answers come, will there be generalizations or will the results arrive piecemeal?

DISCLOSURE STATEMENT

The author is not aware of any biases that might be perceived as affecting the objectivity of this review.

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Wright's clearest exposition of his shifting-balance theory

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