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POPULATION GENETICS HISTORY: A PERSONAL VIEW

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CONTENTS

INTRODUCTION.....	1
MENDEL, HARDY, AND WEINBERG.....	2
EARLY THEORISTS, 1912-1918.....	3
THE THREE GIANTS.....	4
<i>J. B. S. Haldane</i>	5
<i>R. A. Fisher</i>	7
<i>Some Extensions of Fisher's Fundamental Theorem</i>	9
<i>Sewall Wright</i>	10
<i>Who Was Right?</i>	12
TWO NEWCOMERS IN THE 1950s.....	14
MOLECULAR EVOLUTION.....	16
SOME TRENDS IN POPULATION GENETICS.....	18
FINAL REMARKS.....	19

INTRODUCTION

Space limitations dictate that this review be selective, and I have restricted it to the mainline, classical theory. The choice of subjects is arbitrary; they are topics that I think are interesting and historically important.

It is customary, even de rigueur, to point out the great contributions of Haldane, Fisher, and Wright. Indeed, they dominated the field for thirty years and converted it into a new scientific discipline, with mathematical theory, broad generalizations, and quantitative predictions. This review is dedicated to the proposition that the three pioneers constructed a remarkable foundation,

but that the edifice itself is still under construction and the foundation, for all its strength, needs some shoring up.

Various aspects of population genetics have been frequently reviewed in this and related publications (17, 19, 24, 46–50, 53, 80, 81, 97). Provine (75) has written a history of the early years.

MENDEL, HARDY, AND WEINBERG

The beginnings of genetics and of population genetics are one. Both started with Mendel (60); and of course both were unrecognized until the rediscovery in 1900.

In his classic paper Mendel considered the consequences of repeated self-fertilization, a natural line of inquiry since his peas were normally self-fertilized. Mendel showed that heterozygosity is reduced by half each generation and gave formulas for genotypic frequencies in successive generations, starting with an F_1 population derived from two homozygous strains.

Curiously, Mendel did not consider the consequences of random mating, again perhaps because of the breeding habit of his peas. The first to solve this problem, and receive credit for it, was the distinguished British mathematician G. H. Hardy (31). Although the principle is trivially simple, it is nevertheless the foundation for theoretical population genetics. It has two aspects: (a) If there are no genetically determined fitness differences, no migration, no mutation, and no random fluctuations, the allele frequencies do not change from generation to generation. (b) With random mating, the array of diploid genotypes is given by the binomial expansion of the square of the gametic array.

The first aspect is a truism: if no factors are present that change allele frequencies, they don't change. But there is the useful corollary that genotype frequencies can change while allele frequencies do not, as with inbreeding and assortative mating. The second principle is the one that made possible the rapid development of diploid population genetics theory. Zygotes are constructed anew each sexual generation, and when multiple loci are considered, essentially every zygote is unique. Allele frequencies, on the contrary, are relatively stable. This permits the great simplification of regarding allele frequencies as the fundamental quantities for evolutionary change. Since the binomial square principle (or multinomial if there are multiple alleles) relates zygotes to gametes, it does not matter whether the gametic frequencies are genes, linked clusters, chromosomes, or entire gametes. An enormous body of data supports the idea that most gene loci in most diploid populations conform to this principle well enough to make it one of great utility.

It is not surprising that a principle as simple as this has been rediscovered several times. Special cases were published soon after the rediscovery of

Mendelism, and doubtless many geneticists understood the principle without thinking it worth publishing. I once asked Sewall Wright when he had first heard of the Hardy law. His answer was that he had never thought otherwise; he had used the idea before he ever read the Hardy paper.

One other person should be specifically mentioned, Wilhelm Weinberg (82). Weinberg, a German physician, published the binomial square principle the same year as Hardy (86). But, in distinction to Hardy, who did no further work in population genetics, Weinberg went on to many other discoveries. Most important for population genetics were his extension of the principle to multiple alleles and multiple loci, his attempts to reconcile Mendelian inheritance with quantitative traits, his determining the correlation between relatives, and his taking environment into account (87, 88). Like Mendel's, his work went unrecognized for many years. His papers were hard for British and American geneticists to understand, only partly because they were written in German. By the time his work was recognized in the English-speaking world, it had been superseded, especially by Fisher. Weinberg also made basic contributions to the methodology of human genetics. There is at least some justice, for his name is enshrined in genetic history; the binomial square principle is now called the Hardy-Weinberg law.

EARLY THEORISTS, 1912-1918

Before 1918 British geneticists were embroiled in an acrimonious dispute as to whether Mendelism and biometrical genetics were compatible (75). Curiously, and fortunately, the dispute did not carry across the Atlantic. Most early American geneticists—East, Shull, Castle, Wright, Sturtevant, Muller—assumed from the beginning that continuously varying traits were determined by the cumulative effects of Mendelian factors whose individual effects were too small, or too obscured by environmental influences, to be measured.

Most of the early theoretical work in the United States dealt with the effects of inbreeding. The early leader was H. S. Jennings (32-34; see also 11). The pattern, followed by him and others at the time, was to work out arithmetically the genotype frequencies for a few generations and look for a pattern. The danger of such a procedure is obvious. The most egregious faux pas was made by Raymond Pearl (73). Starting with two homozygotes, AA and aa , he correctly calculated that the F_1 are all Aa , and with sib-mating, the F_2 and F_3 are 50% Aa . He then assumed that if two successive generations remained unchanged so would all subsequent generations; ergo, there is no cumulative increase in homozygosity with repeated sib-mating. This conclusion is contrary to the most elementary intuition, and Pearl himself soon corrected his results (74). Nevertheless, such extrapolation was the methodology of the

time, and much of the early knowledge of the effects of systematic inbreeding systems and simple selection was gained in this way. This work pattern came to an abrupt halt when Wright (89) used his correlation (path-analysis) method to produce a simple algorithm to compute the inbreeding coefficient and the decreased heterozygosity for any pedigree or mating system, however complex.

Extension to multiple alleles usually involves no difficulties, but the theory becomes enormously more complicated when more than one locus is considered. Even two loci introduce complications. Both Jennings (34) and Weinberg (87) showed that the approach to gametic equilibrium for two loci is not immediate, as is zygotic equilibrium, but is approached asymptotically. After pages of painful struggling Jennings (34) concluded by saying, "The present writer would find it a relief if some one else would deal thoroughly with the laborious problem of the effects of inbreeding on two pairs of linked factors." The challenge was taken up by Robbins (78), who used methods that, although well known to mathematicians, were not part of the knowledge of geneticists at the time. Robbins formulated a measure of linkage disequilibrium, essentially the same as that used today. It was not, however, until much later that Bennett (1) solved the problem for an arbitrary number of loci. Regardless of the number of loci and for any amount of recombination greater than zero, the frequency of a composite gametic type approaches the product of the constituent allele frequencies. For two loci, the rate of approach is equal to the recombination rate, but for more than two the rate is more complicated. These results apply to an infinite population with no selection; in a finite population or with selection, linkage disequilibrium may be generated.

Jennings (33) also considered simple selection. A more detailed study was made in England at the instigation of R. C. Punnett. He enlisted the help of a mathematician, H. T. J. Norton, who worked out formulas for selection of arbitrary intensity over many generations. Norton prepared tables that listed the number of generations required to change the genotype frequencies from one specified frequency to another. The results appeared in Punnett's textbook on mimicry published in 1915 (77).

Thus, by 1918 the simpler problems of random mating, inbreeding, and selection had been solved.

THE THREE GIANTS

From the end of World War I until the 1950s, Haldane, Fisher, and Wright completely dominated the field. Other contributions were miniscule by comparison, and no doubt the prominence and greatness of these three were inhibiting.

Each of the three had other interests. Wright spent the major part of his time on physiological genetics, especially of pigments, in guinea pigs. Fisher almost single-handedly laid the foundations for modern statistics. Haldane's multifarious activities ranged from politics to fiction writing to astronomy, and included many areas of biology. To a substantial degree their work overlapped. Each was concerned with generality; physics was the paradigm. Yet each had his own style, his own way of looking at problems, and his own view of what was most important. Full-length biographies of all three are available (2, 3, 76); for their personal side, see also (8–10).

J. B. S. Haldane

Haldane started by continuing the studies of Norton. He asked how rapidly the genetic composition of a population would change, given the relative fitnesses of different genotypes. Many of his results were qualitatively predictable, but Haldane quantified them. For example, one would expect an inverse relationship between rate of change and selection intensity, but Haldane demonstrated that for weak selection the number of generations required for any specified change in the composition of the population is proportional to the reciprocal of the selection intensity. He also considered strong selection and showed that the replacement of a light-colored variety of the peppered moth by a more heavily pigmented one as industrial smoke permeated the British landscape required selection intensities of about 50%.

Haldane also showed, for a continuously variable trait, the relationship between the selection differential (the difference between the mean of the selected group and the population average) and the selection intensity (the proportion selected). He noted that most people overestimate the differential for intense selection; for example, saving 1% of the population produces a differential only 51% greater than saving 10%. This relationship has been of great value in livestock breeding by helping the breeder decide how to optimize selection for multiple objectives in species with limited reproductive potential.

One of my favorite Haldane papers (26) introduced the idea of representing a population by a point in an n -dimensional cube, in which the edges represent allele frequencies. Selection moves the population along a trajectory to an equilibrium. Of particular interest are alleles that are favorable in some combinations but unfavorable in others. In a simple two-locus example, used by Haldane, genotypes $aa\ bb$ and $A-\ B-$ are favored by selection, while $A-\ bb$ and $aa\ B-$ are less fit. The situation is illustrated in Figure 1. (The axes are reversed in Haldane's book. His papers are models of clear exposition; but there are frequent errors, I suspect because he worked very rapidly and relied too heavily on an extraordinary, but not quite perfect, memory.)

There is an unstable internal equilibrium, but from any other starting point

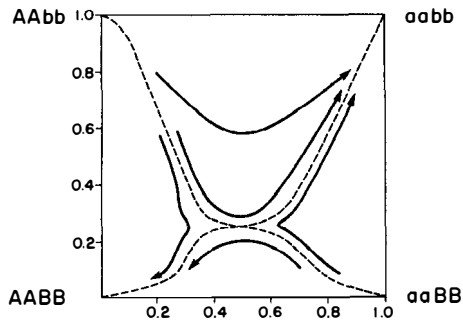


Figure 1 The trajectories of gene frequency change. The abscissa is the frequency of allele a , the ordinate that of b . The relative fitnesses of the four phenotypes are: $A-B-$, 1; $aaB-$, $1-s$; $A-bb$, $1-4s$; $aabb$, $1+11s$. The borders between the four zones are indicated by dotted lines. There is an unstable equilibrium where these lines meet. Modified from Haldane (27).

(and from this one if there is a displacement for any reason) the population will go to fixation of one of the two favored genotypes. The important point is that if $A-B-$ is less fit than $aa\ bb$ and the initial population is mainly $A-B-$, the population cannot get to the more fit situation where $aa\ bb$ predominates. Mass selection of loosely linked genes does not guarantee increased population fitness, a point given great emphasis by Sewall Wright in his shifting balance theory. Curiously, Haldane never included mean population fitness as another dimension in his graph; otherwise he would have anticipated Wright's peaks-and-valleys metaphor.

Haldane's early work is summarized in an appendix to his book, *The Causes of Evolution* (27), from which references to individual papers can be obtained.

Haldane's most original papers, I believe, were those on the effect of variation in fitness (genetic load) and the cumulative cost of an allelic substitution (cost of selection). In his genetic load paper (29) Haldane demonstrated that the effect of recurrent mutation on population fitness does not depend on the deleteriousness of the individual mutations, but only on their rate of occurrence (and on their interaction). For independently acting recessive mutations, the load is simply the gametic mutation rate and for partially or completely dominant mutations, twice this value.

The Haldane load principle was later discovered independently by Muller (67). Haldane also showed that the load involved in maintaining an overdominant locus (the segregation load) is much larger than the mutation load for a classical locus with intermediate or complete dominance. This observation seemed to offer a way to distinguish between the importance of loci of the two types, leading to a controversy in the 1960s that I have reviewed elsewhere (12). The main difficulty with load theory in setting a realistic limit on the

total mutation rate or number of segregating overdominant loci is that truncation selection, by permitting multiple mutants to be eliminated by one genetic death, renders the principle much less restrictive (15, 44, 61, 84). It may be possible to use load theory for human mutation risk assessment and at the same time eliminate some of its faults by measuring the "mutation component" (13).

Haldane's genetic load is a measure of the loss of fitness due to static variation—recurrent mutation, heterosis, epistasis, and environmental mismatches. It is the cost of maintaining the status quo. The second Haldane principle, the cost of selection, is dynamic; it is the cost of changing (30). This principle offers at least a partial quantification of the fact, painfully apparent to the breeder, that there cannot be simultaneous strong selection for several independent traits. The cost of a favorable gene substitution has the property, similar to that of the mutation load, of being independent of the magnitude of the change. Haldane showed that the cumulative loss of fitness, compared to that of the population after the favorable allele has been fixed, is a function of its initial frequency. Haldane suggested that, as a typical example, to substitute one allele every 300 generations would require a reproductive excess of about 10%. This, he thought, would place some sort of limit on the rate of evolution. As with the load principle, Haldane did not really come to grips with multi-locus interactions. (For a review of load and cost principles, see 5.)

R. A. Fisher

Fisher augmented his already great mathematical and statistical skills with a remarkable creative faculty. His work has an elegance not found in the writings of either Haldane or Wright. On each rereading of *The Genetical Theory of Natural Selection* (22) I am again impressed by his clever insights, often tossed off as throw-away lines in his book. Fisher's first great contribution was reconciling Mendelian inheritance with biometry, showing that the correlations between physical measurements of close relatives were well in accord with Mendelism (20), which the early biometricians had denied. Weinberg had already realized that deviations from perfect correlation with the proportion of shared genes could be caused either by dominance and epistasis or by environmental effects. Fisher went further and showed that dominance contributes to the sib correlation but not to that of parent and offspring. In principle, this permits dominance and environmental effects to be separated. Fisher undoubtedly erred, however, in attributing the greater sib than parental correlation in height entirely to dominance rather than to the greater environmental similarity of sibs. Although Fisher's 1918 paper is a masterpiece and one of the foundation stones for quantitative genetics, it was an anticlimax in so far as its main purpose was concerned. By the time the

paper appeared—it was unfavorably reviewed and its publication was delayed more than two years—Mendelism had already been widely accepted as a sufficient explanation of metrical traits, especially in the United States, where it had never been seriously questioned. But the mathematical foundations of genetic analysis of quantitative traits were laid.

Fisher placed great emphasis on the variance-conserving property of Mendelism. He noted that, with blending inheritance and random mating, variance is reduced by half each generation, thus requiring (as Darwin realized qualitatively) an enormous input of new variability. With Mendelism, on the contrary, a small amount of mutation is sufficient to maintain a large standing variance in all but very small or inbred populations. The problem is the reverse of what Darwin thought. Instead of a problem in accounting for the amount of observed variability, there is the opposite problem of deciding the relative importance of several factors, each of which is sufficient. Fisher also argued forcefully for evolutionary gradualism, noting that the larger the effect of a mutant gene the greater its chance of being highly deleterious and therefore of no long-time evolutionary consequence. In this belief in Darwinian gradualism—that large evolutionary changes were the accumulation of small changes, and not a single saltation—Fisher was joined by Haldane and Wright. On this point their agreement was emphatic.

Fisher (21) showed for the first time the principle, now regarded as obvious, that selection in favor of the heterozygote leads to a stable gene-frequency equilibrium. He also showed how to include the accidents of gene-sampling that occur during reproduction in finite populations, although, contrary to Wright, he placed little emphasis on this.

Haldane's writings for the most part ignored epistasis. Although his views were not necessarily so simple, his mathematical work on evolution dealt mainly with the successive substitution of favorable mutations. Fisher, in contrast, specifically took dominance and epistasis into account. His great contributions were realizing that natural or artificial selection for any character acts on the additive, or genic, component of the genetic variance of that character, and showing how to extract this component by various measures, such as correlations between relatives. In nature, where the all-important character is fitness, this is summarized by his Fundamental Theorem of Natural Selection: "The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time." By genetic variance he means additive or genic variance. Fisher made it clear that this is a measure of fitness increase due to gene-frequency change relative to conditions at the time. Most such change is offset by overcrowding and changes in the environment, and there may be deviations from the theorem caused by changes in heterozygosity, linkage relations, and age structure, and by frequency-dependent fitnesses. Some of these factors have been introduced explicitly

into the theorem by Kimura (38). Kimura's treatment has been widely regarded as clarifying and extending Fisher's theorem. But, characteristically, Fisher regarded his original statement as complete and not in need of either clarification or extension.

To me, this idea initiated by Fisher is a remarkable synthesis. It is obvious that the rate of evolutionary change depends on the amount of variability, but it is not obvious that the appropriate measure of variability is the mean square deviation, or variance (a name that Fisher himself coined in his 1918 paper). It is also not obvious that the additive component of the variance, extracted by least squares estimation, yields that variance component that is responsive to selection.

Leigh (47, 48) has written an insightful review of Fisher's evolutionary theory.

Some Extensions of Fisher's Fundamental Theorem

There are three interesting extensions of Fisher's theorem. The first, due to Robertson (79), states that the rate of change of a character correlated with fitness is the additive genetic correlation of this trait with fitness. It permits predictions from selection on traits other than fitness itself from knowledge of the correlation of such traits with fitness (16).

The second extension is a remarkable property discovered by Kimura (40; 14, p. 217 ff). Fisher (20) had shown that although dominance variance does not contribute to parent-offspring correlations, epistatic variance does. When there is epistasis, selection generates linkage disequilibrium. Kimura showed, however, that the degree of disequilibrium soon reaches a nearly stable amount as gene frequencies slowly change. When this stage is reached the measure of disequilibrium is opposite in sign to the epistatic variance, and these two factors approximately cancel, leaving only the genic or additive variance as the measure of fitness change. Natural selection produces just enough linkage disequilibrium to balance the epistatic variance. Thus, in long-continued directional selection, natural selection manages to select on the basis of average effects of genes, not on their interactions. The most important exception to this rule is strong epistasis combined with close linkage. In this case the linked cluster behaves almost like a single gene. Intermediate values of linkage and epistasis require a more detailed treatment.

The third extension is a Haldane-like idea. The major defects in the Haldane cost of selection as a rate-limiting factor in evolution are that it is measured as a deviation from ultimate fitness and that it fails to include properly the effects of epistasis. It has seemed to me that there is another way of determining the extent to which genetic variability limits evolutionary progress (6). This equation is like the Haldane cost because it sums the effect over several generations and like Fisher's theorem because it is measured in

terms of variances rather than means. We ask for the amount of variance required to increase the mean fitness by an amount S . Using the Fisher theorem, and letting w stand for fitness and V_g for genic variance, we can write an approximate formula for the change in mean fitness in one generation:

$$\Delta \bar{w} = V_g, \text{ and therefore } S = \Sigma \Delta \bar{w} = \Sigma V_g.$$

So to change the mean fitness by amount S requires a total variance of this same amount, regardless of the time required. The change can be rapid, with the variance used up quickly, or slow if it is distributed over many generations.

Assume that 10^4 loci are evolving at a rate roughly that of hemoglobins, or 2.5×10^{-6} per generation. Assume further that each substitution confers a selective advantage of 0.01, and by the principle above involves a total genic variance of 0.01. The total genic variance required to evolve at this rate is $10^4 \times 2.5 \times 10^{-6} \times 10^{-2} = 2.5 \times 10^{-4}$. This is a very small amount. The genic variance for viability alone in *Drosophila* is about 0.01 (65). There appears to be more than enough additive variance to account for observed evolution rates. Although the example I have given is one in which alleles are independently substituted, the principle still holds if there are interactions.

Sewall Wright

Sewall Wright's shifting-balance theory grew out of his studies on guinea pig coat color, his observations of the effects of inbreeding, and his analysis of the history of domestic livestock. Coat-color genetics convinced him that epistatic interactions are common and complex. Gene combinations often give results that would not have been predicted from the single-gene effects, and that could render selection toward a particular color ineffective. His studies of inbreeding showed that the different strains acquired different characteristics, as a result of random fixation of alleles that were segregating in the foundation stock. Finally, he studied the history of domestic animals, especially Shorthorn cattle, for which extensive records were available. He astutely noticed that the overall improvement of the breed took place, not by selection within herds, but between herds. A particular herd would turn out to have exceptionally fine animals, seemingly largely by chance rather than by selection within the herd. From such herds bulls were exported and by repeated backcrossing other herds were "graded up" to the quality of the imported bulls.

Wright was especially impressed by epistatic combinations such as those I mentioned earlier in which unfavorable individual components lead to an improvement in combination. Yet there is no way to reach this endpoint by

mass selection. Wright thought of this in his now-famous peaks-and-valleys metaphor. For two loci, each with two alleles, we can think of each allele frequency combination as a point in a unit square in which the scales on the sides are the allele frequencies at the two loci. This square is the same as that on which Haldane plotted the trajectories shown in Figure 1. If we take this unit square and erect at each point an ordinate proportional to the mean fitness of a randomly mating population with this combination of allele frequencies we have a Wrightian fitness surface. [Provine (76) has argued that the meaning of Wright's abscissas is fuzzy; and indeed Wright's early writings are not explicit on this point. It is clear, however, that the most transparent and useful interpretation is the one I have just given, in which the abscissas are allele frequencies, as in Haldane's diagram, and more recently Wright has adopted this interpretation. Wright tells me that although he read Haldane's paper, he had thought of the peaks-and-valleys metaphor quite independently.]

The highest peak occurs at the upper right, with a lower one at the lower left. There is a saddle point where the zone borders meet. From the trajectories we see that a population near the lower left corner tends to move toward that corner. Unless the gene frequencies somehow jump past the boundary into the upper right zone, the population cannot reach the higher fitness peak at the upper right corner. To Wright the essential dilemma is how a population can evolve from one harmonious gene combination to a better one, when intermediate combinations are discordant.

One possibility is for the genes to be closely linked, but nature cannot count on favorable combinations happening often to be linked. The best solution, according to Wright, is a population structure that permits a certain amount of local differentiation. If there are many subpopulations there is a chance that one of them will randomly drift into a high frequency of a favorable gene combination. This population will then grow more rapidly than the others and send out migrants, in the manner of bulls being exported from outstanding herds of cattle (or perhaps African bees moving through Central America). In this way Wright visualizes the gradual upgrading of the species as a whole. Then, after subsequent subdivision, the process can be repeated.

Fisher and Wright therefore arrive at opposite conclusions regarding the kind of population in which evolutionary progress is optimized. For Fisher, dominance and epistasis are facts of life, but decrease the rate of response to environmental changes, since natural selection acts on the additive component. Natural selection is most effective in a large panmictic population where variability is great and random noise is minimal. If the environment remains constant, the population is not far from the optimum combination of allele frequencies at any one time. But the environment will not remain constant, if for no other reason than that competing species continue to

change. If the environment changes, a large population has sufficient variability to adapt quickly to the new conditions. Fisher thought that environmental changes are so ubiquitous that, as he once said, Wright's peaks and valleys are more like the undulating wave crests and troughs of an ocean than a mountainous landscape. He believed that a population rarely, if ever, finds itself in a position where *no* allele frequency change could increase its fitness.

For Wright, gene interaction is not simply a nuisance impeding the rate of allele frequency change; rather, it is a part of evolutionary creativity. In his view, epistatic hangups are common enough to constitute a major barrier to progress under mass selection. Only some means by which favorable combinations can be put together will solve this dilemma. Wright's theory calls for a rather delicate balance of migration rates, selection differences, and local deme sizes. The between-group selection that occurs when a favorable combination arises must not permit much mixing of groups, lest recombination destroy the very combinations that are the basis for the one group's superiority. But Wright does not argue that his process happens regularly or often, only that important evolutionary advances depend on such a situation.

There the argument stood in the 1930s, and there it stands today. Fisher held to his views until his death in 1962. Wright's views have remained essentially unchanged; compare his 1931 paper (90) with one of his latest (97). In his later years Wright wrote four volumes summarizing his, and much other, work (93–96). He was 97 in December 1986, and as recently as March 1987 sent a long manuscript to Provine defending his fitness surface diagrams.

Who Was Right?

We must remember that Fisher was mainly interested in how an organism can increase its fitness, or rather how it can maintain its fitness position on the treadmill of a continuously worsening environment. He didn't especially care what biological structures or processes this involved; the important trait is fitness, however it is achieved. Wright, on the contrary, is interested in evolutionary progress or novelty, not simply fitness adjustment. They may both be right.

My own view is that the large area of agreement between Fisher and Wright has had insufficient emphasis. They were in complete agreement about the importance of polygenic inheritance and individually small effects. They agreed that a great deal of natural selection consists of keeping up with changes in the environment. Both thought that much of evolution depends on quantitative traits, and that such traits usually have an intermediate optimum.

It was clear to both Wright and Fisher that in a panmictic sexual population, selection acts on the additive component of the genetic variance (genic selection). An asexual population, in which selection can act on the total

genetic variance (genotypic selection), could well have an important advantage. Yet both regarded the ubiquity of sexual reproduction with its attendant Mendelian inheritance as an argument that Mendelism is of great evolutionary benefit. One could describe Wright's model, with its combination of intragroup random drift followed by intergroup (genotypic) selection, as a way of bringing some of the benefits of asexual reproduction to a sexual species.

Recent research has demonstrated that genes with very small effects tend to have incomplete dominance and little epistasis; in particular this is true for those affecting fitness (7, 66). Polygenic inheritance has the evolutionarily useful property of having a large potential variance with a small standing variance. Selection toward an intermediate phenotype, especially when the fitness function is concave, maintains substantial variance on the primary scale with relatively little on the fitness scale. If the optimum value changes because of a changed environment, the population has a large additive variance by which to move the mean to the new optimum. That this mechanism exists in nature and is sufficient for much of fitness evolution is, I think, clear. It is possible that the extreme epistasis that Wright found for guinea pig coat colors is not typical of genes, probably mostly regulatory, having minor effects on fitness. I regard the ubiquity of sexual reproduction as an argument that a great deal of evolution depends on genes that are roughly additive. Wright and Fisher agreed that much of evolution, such things as keeping up with changing environments and evolutionary fine-tuning, is of this type.

If there is to be evolutionary fine-tuning, two conditions are required (52). One is a certain amount of continuity; if a little bit of something causes a phenotypic change in a certain direction, a little more should ordinarily continue in the same direction. The other is a certain independence; it must be possible to adjust one character without adversely affecting others. In these regards, organisms are not like computers where an error in one part often upsets the whole thing. Carrying computer analogies into biology has, I believe, mistakenly led some to doubt the sufficiency of mutation and natural selection as a mechanism for evolution (62). Clearly nonindependence and discontinuities occur, but perhaps those sexual organisms that have survived the evolutionary struggle are those in which these impediments have not been overwhelming. Those species that have opted for an asexual mode of reproduction may be preserving a particularly happy gene combination that would be broken up by recombination.

So, it seems to me, we know that most adaptive changes, adjustment to environmental changes, and fine-tuning occur under the Fisher model. One must not forget some coadapted complexes, locked into an inversion or very tightly linked, and often polymorphic, as Fisher himself emphasized. But in most sexual species this must be a minor part of fitness adaptation. The

question remains whether evolutionary novelty requires something more, as Wright believes. As long ago as 1932, Haldane (28) said:

It would seem that we must envisage the possibility that there are two rather different types of evolution. The first, primarily studied by the paleontologist, is that of dominant species in a fairly stable environment. Such species change slowly by the gradual spread of genes, each with a relatively slight effect. . . . The second type is characteristic of species whose members exist in quite small and nearly or quite isolated groups. Such a group may undergo a cytological change or a change in several genes at once. Such changes, while they must ultimately stand the test of natural selection, are not themselves due to natural selection.

It's a very Wrightian statement.

Wright, although agreeing that the Fisher mechanism may account for most fitness change, believes that the evolution of novel processes and structures requires something more. He notes that major evolutionary innovations have left a weak fossil record, as if they occurred in populations that were sparse—thus favoring local differentiation. A strong argument in favor of the Wright view is that groups with various rapid evolutionary innovations, such as the mammals, have also had a large number of cytogenetic changes, such as translocations. If such cytogenetic changes occurred in a large panmictic population, there would be selection against individuals heterozygous for the arrangement. The result argues for the importance of some sort of random process in the evolution of novel types.

It may be that this is too big a question to be answered any time soon. We need to know not only what is the optimum structure, but what is the actual structure. This will depend on detailed case-by-case analysis. But we can count on more and better information about actual population structures and about the extent of gene interaction. One difficulty is that Wright's arguments become verbal, rather than mathematical, just at the point where the theory becomes controversial. We can surely expect modern developments in mathematics and computer technology to lead to a theory that is deeper, more rigorous, more powerful, and more predictive. Then perhaps we shall have an adequate test of Wright's appealing theory.

TWO NEWCOMERS IN THE 1950s

Haldane, Fisher, and Wright dominated the field of population genetics for the first half of the twentieth century. But in the early 1950s things began to change. Some new names appeared on the scene.

Gustave Malécot was a distinguished French mathematician who brought a new level of mathematical power to population genetics. He published his work in journals that, although not always obscure, were not ordinarily read by population geneticists; furthermore, he wrote in French. The combination

of linguistic and mathematical difficulties made his work inaccessible, even to those who were aware of it. His thesis, published in 1939 (54), follows the pattern of Fisher's 1918 analysis of correlation between relatives. It is notable for attention to assumptions and details that Fisher glossed over.

I first became acquainted with his work through a short 63-page book, *Les Mathématiques de l'Hérédité*, published in 1948 (56; for an English translation see 58). I still remember the excitement it brought. It had a clarity and logic that I had not seen before in problems of relationship and inbreeding. Although I was already familiar with Malécot's simpler results because of Wright's work, his concept of identity by descent permitted a clear and elegant derivation of all the standard formulas. With his formulation it was easy to introduce mutation into the process, thus measuring the consequences of finite populations over long times. He also introduced the coefficient of kinship (*parenté*), the probability that two alleles, one drawn at random from each of two individuals, are identical by descent. For the study of natural populations this probability is more suitable than Wright's earlier coefficient of relationship (89). The coefficient of kinship has permitted more realistic models of migration, isolation by distance, and the relationship between kinship and distance. It has been a most useful supplement to Wright's procedures based on correlation analysis and has been widely used (59, 71).

Malécot introduced the idea of population transformations as a Markov chain, which brought in the tools of modern probability analysis (55, 57). He was also influential in developing ways of studying population structure. In particular he found a simple relation between geographical distance and kinship. This formulation has been useful in the study of human populations, especially in the work of Morton and his colleagues (64).

The concept of identity by descent and a probabilistic approach to problems of inbreeding and relationship were independently introduced by Cotterman (4) in an unpublished thesis. By the time it became known, however, the concept had already been presented by Malécot. Furthermore, Cotterman did not consider geographical structure, the subject in which Malécot's methods have been particularly useful.

I may have had some influence in bringing Malécot's work to the attention of English-speaking geneticists by introducing his notion of identity by descent to a summer statistical conference at Iowa State University in 1952 and suggesting him as a speaker for the 1955 Cold Spring Harbor Symposium. Newton Morton, who was associated with me at the time we both first encountered Malécot's work, has been particularly effective in bringing his contributions to the attention of human population geneticists.

Motoo Kimura also first gained recognition in the English-speaking world in the early 1950s. His first paper published in *Genetics* (35) was a thorough analysis of random drift created by variation in selection coefficients, a

problem on which Wright had also worked. I saw the manuscript and was greatly excited by it, as was Wright. Kimura had found a transformation that converted the equation into a form similar to that for heat conduction, and therefore it could be readily solved. Soon after, he showed the distribution through time of allele frequencies in a finite population (36). Wright (92) had shown earlier that his gene frequency distributions could be expressed in terms of the Kolmogorov forward equation. He had solved only the equilibrium distribution. Kimura then proceeded to work out the distribution through time from any arbitrary starting point. The work of Malécot, and especially of Kimura, attracted attention of mathematicians such as Samuel Karlin, and the result has been a much higher level of mathematical sophistication in the field. Another mathematician who became interested in population genetics about this time was Moran (63).

There is not space to review Kimura's voluminous contributions; some of the early work has been summarized (43). But I will emphasize one part. Kimura was especially creative in using the Kolmogorov backward equation. The forward equation gives the distribution of allele frequencies at some future time, given the starting values. The backward equation gives the distribution of starting values for a specified end result. With appropriate identification and boundary conditions, Kimura was able to compute, with greater accuracy than before, the probability of ultimate fixation of a mutant (37). Although it attracted little interest at the time, this computation turned out to be beautifully preadapted for the study of molecular evolution.

MOLECULAR EVOLUTION

The rich stochastic theory of population genetics has until recently suffered from the fact that it deals with allele frequencies, whereas the observations are on phenotypes, often complex ones. Molecular studies, first at the protein level and then direct DNA determinations, have totally changed this imbalance. The data applicable to this theory have been made available. The subject has changed from one that is rich in theory and poor in data to one that is almost the opposite.

The discoveries that there is much more DNA than is required for the expected number of proteins and that the bulk of the DNA has no obvious function have called into question the primacy of selection in determining molecular evolution and polymorphism. The first measures of isozyme variability made it appear that a large fraction of loci were polymorphic and that average heterozygosity was high, perhaps 40% or more (51). This observation immediately raised the possibility that a large segregation load was involved. Several people suggested that one way out of this apparent dilemma was provided by the hypothesis that much of the variability was essentially

neutral. However, increasing data (72) have shown that the early extrapolations were too high and that the average level of heterozygosity per locus is in the vicinity of 5 to 10%, reasonable on a mutation-selection balance model.

The first suggestion that considerable molecular evolution was caused by mutation-driven neutral substitutions came from Freese (23) and Sueoka (83). Both were impressed by the large differences in base ratios in different bacterial species despite similar amino acid makeup, and independently suggested that biased mutation rates and neutrality, together with synonymy of the code, could account for the differences. Recent support of this idea has come from the more extreme base-ratio differences in noncoding and synonymous nucleotides (68).

The random drift hypothesis was first suggested by Motoo Kimura (41). His first paper used the Haldane cost principle to argue that the total amount of DNA substitution was so great as to produce an unacceptable fitness reduction. Quite independently the neutral idea was suggested by King & Jukes (45). In the years since that time the argument has been strongly defended by Kimura. In the process the theory has been greatly refined (42).

The key quantity determining the rate of molecular evolution is the probability of ultimate fixation of a new mutant. The first person to work on this problem was Haldane (25), who, using a method suggested by Fisher (21), showed that the probability of fixation of a new mutant with selective advantage s is approximately $2s$. This was later refined by Fisher (22) and Wright (90) to give the value $2s/(1 - e^{-4Ns})$, where N is the population number.

The formula was further generalized by Wright (91), Malécot (57), and finally by Kimura (37, 39), for any level of dominance, any initial frequency, and fluctuating selection coefficients, and taking into account the likely difference between census population number, N , and effective population number, N_e . For a partially or fully dominant gene the probability is $[1 - \exp(-2N_e s/N)]/[1 - \exp(-4N_e s)]$ or, when s is small and $N_e s$ is one or more, approximately $2s(N_e/N)$. For a recessive the value is $\sqrt{(2s/\pi N)}$. For a neutral allele ($s = 0$), the value becomes $1/2N$, as would be expected.

Kimura's work is much more than a refinement of the formula. He was the first to perceive that the relevant quantity for molecular evolution is the probability of fixation, not the time required for fixation of an individual mutant. For, if we view the process over a time scale that is long relative to the time required for an individual fixation, we need only count the number of substitutions that happen during the period; the time required for each is irrelevant.

The neutral theory has generated a great deal of controversy and a plethora of theoretical and experimental work. This is not the place to attempt a

review. It is abundantly clear, however, that evolution, as observed at the nucleotide level, is following rules different from those of morphological and physiological evolution. The neutral hypothesis has opened up a whole new area for theoretical and experimental work. The connection between molecular, fitness, and morphological evolution remains to be clarified.

SOME TRENDS IN POPULATION GENETICS

Population genetics theory in the past has been dominated by attempts to find the broadest generalizations. This viewpoint especially characterized the theories of Wright, Fisher, and Haldane. Much of the experimental work, when it was related to theory at all, had similar broad aims; as a result it was often inconclusive. Recent trends, both in theory and experiment, have been toward a more detailed, case-by-case analysis.

One trend is toward a steady improvement in rigor. Mathematicians such as Karlin, Moran, Watterson, Ewens, and Nagylaki, following the trends started by Malécot and Kimura, have changed the character of the field. The study of inheritance and evolution of quantitative traits is still based largely on methods of Wright and Fisher. Some improvement in rigor was introduced by Malécot (54), but there is much more to be done. Characters with intermediate optima are of great importance, but the role of mutation and selection in determining phenotypic variance is not fully understood. According to one model, the fitness is reduced in proportion to the square root of the mutation rate; according to another it is proportional to the mutation rate. A major step toward a resolution of this seeming paradox was provided by Turelli (85), who showed that the two models represented opposite ends of a continuum of necessary assumptions about mutation rates. Another area where work at the very foundations is needed is in geographical structure. Still another is the accuracy of diffusion approximations, especially as the allele frequency approaches zero or one.

Another kind of work that seems particularly important to me is a careful assessment of the accuracy of the simple formulas now in standard use. The idealized models under which the formulas were derived are never exactly true. The question is: how robust are these formulas to departures from the idealized assumptions? The leader in studying this is Nagylaki (69, 70). His work has been reassuring in showing that standard equations, derived from the simplest assumptions (e.g. discrete generations, multiplicative fertility), are excellent approximations to a more realistic situation. More importantly, he has shown how to determine the magnitude of error involved.

Finally, there is a whole new theory being developed for the newer findings of molecular biology and their bearing on evolution. One example is the study of multigene families. Another is research on transposable elements. These

are currently active fields of investigation as the theory is developed to fit the rapid growth of new facts.

FINAL REMARKS

My concluding remarks are very similar to those expressed by Ewens (18, p. 33). The “golden age” of population genetics was the period when Haldane, Fisher, and Wright were producing their great work. They reconciled biometry with genetics, quantified the approach to evolution, and created a totally new science. It was arguably the most successful mathematical theory in biology.

The period around 1960 marked the end of the beginning. Like the early theories in physics, population genetics in the golden age was rough and ready. By modern mathematical standards it lacks precision and rigor. We can expect that the foundations will be solidified. A likely result is that this will prove that what we think we know is correct, and that is good in itself; but there will be surprises. There are also new developments in the theory, carrying it in new directions. Some of this will deal with special items—mitochondrial evolution, meiotic drive, multigene families, transposons, viruses. These need to be integrated into the overall theory, with the objective of a deeper understanding of the relative importance of these compared to classical processes as evolutionary forces.

Molecular biology has enormously enriched the field. So has the neutral theory, by bringing in a revolutionary new concept. No longer can one treat molecular evolution without stochastic considerations.

The connections between molecular, fitness, physiological, and morphological evolution are now obscure. A major task for the future is to fit these together. As experimental techniques improve, I think we can also count on a closer coordination of experiment with theory than has characterized the field in the past.

In his 1932 book (27), Haldane closed his mathematical appendix with this statement: “The permeation of biology by mathematics is only beginning, but unless the history of science is an inadequate guide, it will continue, and the investigations here summarized represent the beginning of a new branch of applied mathematics.” He was right.

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