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5 Population Genetics: The Synthesis of Mendelism, Darwinism, and Biometry

When Charles Darwin first envisioned the process of natural selection he believed firmly that a population naturally produced much new heritable variability each generation. He also believed in blending inheritance, which was nature's way of keeping a species true and uniform despite this new variability each generation. Thirty years later he finally designed his provisional hypothesis of pangenesis to account for the production of sufficient variability to make natural selection possible, even though blending inheritance tended to obliterate the variability. But Darwin's theory of pangenesis was never very successful, and the most basic weakness of his concept of evolution was the lack of an adequate theory of the production of the variations upon which natural selection acted. Mendel's theory of heredity was the perfect complement to Darwin's idea of natural selection. Mendelian characters could be very small and were not blended away by crossing. Furthermore, Mendelian recombination provided new variability for selection. When Mendelian heredity was rediscovered, however, for a variety of scientific and personal reasons, it became associated with the mutation theory of evolution rather than with Darwin's idea of continuous evolution. One consequence of this association was that as Mendelism gained attention in the first decade of this century, Darwin's idea of natural selection lost attention. But by 1918, primarily as a result of the analysis of successful selection experiments, many geneticists had realized that Mendelian heredity and Darwinian natural selection were complementary. The study of evolution, however, required more than the general recognition that Mendelism and Darwinism were complementary. It required a careful investigation of the evolutionary consequences of Mendelian heredity. Under a given set of assumptions the mathematical consequences of

Mendelian inheritance could be computed. Thus the study of evolution required a synthesis of Mendelism, Darwinism, and biometry. The basic elements of this synthesis were carried out by R. A. Fisher, J. B S. Haldane, and Sewall Wright.

Exploration of the Mathematical Consequences of Mendelian Heredity before 1918

Three developments before 1918 in the exploration of the mathematical consequences of Mendelian heredity influenced the work of Fisher, Haldane, and Wright. The first of these was the (later named) Hardy-Weinberg equilibrium principle, which was of basic importance for population genetics because it guaranteed that variability was preserved in random breeding Mendelian populations. The second was the work on the mathematical consequences of inbreeding carried out primarily in the United States. This work influenced Sewall Wright, who later supplied a powerful analysis of the quantitative aspects of inbreeding. The third development was the analysis of the effects of selection prepared by the mathematician H. T. J. Norton and published in a book by R. C. Punnett. Norton's work stimulated both J. B. S. Haldane and the Russian geneticist Chetverikov to examine further the mathematical consequences of selection under a variety of assumptions about the constitution of the population. These three developments were independent but are here treated together because they partially formed the foundation for the work of Fisher, Haldane, and Wright.

The Hardy-Weinberg equilibrium principle

The first person to explore the mathematical consequences of Mendelian heredity was Mendel himself. In the paper describing his experiments with peas, in a section entitled "The Subsequent Generations [Bred] from the Hybrids," he calculated the effects of continued self-fertilization on the genetic constitution of a population. Starting with a population formed by the hybridization of races AA and aa, he found as a trial and error generalization that in the nth generation of self-fertilization the ratio of genotypes was $(2^n - 1)AA : 2Aa : (2^n - 1)aa$. Continued self-fertilization clearly led to increas-

ing reversion to the parental types *AA* and *aa*, and to the decrease of heterozygotes.

The next logical step would have been to calculate the effect of Mendelian inheritance for a single locus with two alleles in a random breeding population instead of one which was self-fertilized. Mendel published no analysis of this problem. Had he considered the problem, he probably would have derived the Hardy-Weinberg equilibrium principle. After the rediscovery of Mendelism the first investigator to look at the consequences of Mendelian heredity in a random breeding population was Yule in 1902. He first supposed the existence of two races, one pure for the dominant character *A* and the other pure for the recessive character *a*. Then he asked:

> What, exactly, happens if the two races *A* and *a* are left to themselves to inter-cross freely *as if they were one race?* . . . Now when *A*'s and *a*'s are first inter-crossed we get the series of *uniform* hybrids; when these are inter-bred we get the series of three dominant forms (two hybrids, one pure) to one recessive. If all these are again inter-crossed at random the composition remains unaltered. "Dominant" and "recessive" gametes are equally frequent, and consequently conjugation of a "dominant" gamete will take place with a "recessive" as frequently as with another "dominant" gamete.[1]

Yule recognized the stability of the $1AA:2Aa:1aa$ ratio in a random breeding population. And his method of looking at the population as a gene pool was later widely used in population genetics. He neglected to mention that at this time he believed the 1:2:1 ratio was the *only* stable equilibrium for the gene frequencies, that is, when *A* and *a* were equally numerous in the population.

Yule's paper elicited a response from William Castle in the United States. Castle read the section in which Yule showed the stability of the 1:2:1 ratio and mistakenly thought Yule had claimed that selective elimination of all recessives each generation did not lead toward complete homozygosis in the population. Yule had said no such thing. But with this stimulus, Castle attacked the problem of gene frequencies under random mating. First he agreed with Yule about the stability of the 1:2:1 ratio. Then he showed that the complete elimination of recessives each generation did lead toward homozygosis. This was obvious and Yule would surely have agreed. He also made the conclusion (and here Yule would have disagreed, though this was not clear from his 1902 paper) that "as soon as selection is arrested the race remains stable at the degree of purity then attained."[2] In nonmathematical terms, this was the generalized equilibrium principle for a single locus with two alleles in a random breeding population.

1. Yule, "Mendel's Laws and Their Probable Relations to Intra-racial Heredity," p. 225.

Karl Pearson read the papers of Yule and Castle on the mathematical consequences of Mendelian heredity. In 1904, starting with the assumption that two equally numerous races *AA* and *aa* were randomly bred together, he worked out the equilibrium principle for a single locus with two alleles.[3] He could easily have demonstrated the general result for any initial gene frequencies, instead of $0.5A$ and $0.5a$, but he did not. He did generalize, under the original assumptions, to the case of *n* loci. He concluded:

> However many couplets we suppose the character under question to depend upon, the off-spring of the hybrids—or the segregating generation—if they breed at random *inter se*, will not segregate further, but continue to reproduce themselves in the same proportions as a stable population.[4]

Pearson was right that a stable equilibrium existed for *n* loci, but he was wrong that the equilibrium was reached in one generation except for the case $n = 1$.

G. H. Hardy's well-known proof of the equilibrium principle came as the result of a curious encounter. In 1908 R. C. Punnett delivered an address at the Royal Society of Medicine on "Mendelian Heredity in Man."[5] In the subsequent discussion Yule suggested that a dominant allele, once introduced

2. Castle, "The Laws of Heredity of Galton and Mendel," p. 337.
3. Pearson, "On a Generalized Theory of Alternative Inheritance, with Special Reference to Mendel's Laws," pp. 58–60.
4. Ibid., p. 60.
5. For Punnett's account of this address, see his "Early Days of Genetics," p. 9.

into the population, would increase in frequency until reaching stability at 0.5, giving the usual phenotypic ratio 3 dominant:1 recessive thereafter. Punnett knew Yule had to be wrong but did not see how to prove it. He took the problem to his friend Hardy, with whom he formerly played cricket. Hardy immediately derived and published in *Science* on 10 July 1908 the conditions for a stable equilibrium in the case of a single locus with two alleles under random mating.[6] Given that the frequency of genotype $AA = p$, of $Aa = 2q$, and of $aa = r$, he showed that the condition for a stable equilibrium was $q^2 = pr$. The condition for a stable equilibrium was always established by a single generation of random mating; so the distribution would remain unchanged in succeeding generations.

The other independent derivation of the Hardy-Weinberg equilibrium principle was of course given by Wilhelm Weinberg (1862–1937), a German physician who devoted considerable energy to the study of human genetics.[7] He became acquainted with Mendelism in 1905 and decided to see if he could find a character in man which was inherited in a Mendelian fashion. Having conducted numerous twin studies before 1905, he suspected the ability to bear dizygotic twins was a Mendelian trait. In a paper read on 13 January 1908 he derived the general equilibrium principle for a single locus with two alleles.[8] Thus he anticipated Hardy by almost six months with this derivation. He calculated the expected frequencies if the twinning trait were dominant or recessive, and decided his data showed the trait was a Mendelian recessive. The Hardy-Weinberg law, once enunciated, was accepted by all Mendelians. It was an obvious deduction from the mechanics of Mendelian heredity. Because Weinberg's papers were ignored,

6. "Mendelian Proportions in a Mixed Population," *Science*, n. s. 28:49–50.

7. For a short account of the life and work of Weinberg, see Curt Stern, "Wilhelm Weinberg," *Genetics* 44 (1962): 1–5.

8. Wilhelm Weinberg, "Ueber den Nachweis der Vererbung beim Menschen," *Jahreshefte des Vereins für Vaterländische Naturkunde in Württemburg* 64 (1908): 368–82. English translation in Samuel H. Boyer, *Papers on Human Genetics* (Englewood Cliffs, N.J.: Prentice-Hall, 1963), pp. 4–15.

the law was for many years known to geneticists as "Hardy's Law."

Weinberg did not stop with the equilibrium principle which now carries his name. In 1904 Pearson had concluded that Mendelism was incompatible with observed correlations in human populations. Weinberg attempted to demonstrate that Pearson was wrong. In 1909 and 1910 he published three other papers on the mathematical consequences of Mendelian heredity with special reference to human genetics.[9] He derived the correlations to be expected between close relatives on the basis of Mendelian inheritance for several cases and made quantitative provision for environmental influences. Fisher, unaware of Weinberg's work, was to make similar calculations in a paper published in 1918. Weinberg extended the equilibrium law in random breeding populations to cover the case of a single locus with multiple alleles. He also extended the law to more than one locus and discovered that equilibrium was not attained in a single generation as Pearson had concluded.

Unfortunately, as mentioned above, Weinberg's papers were ignored by geneticists. Few Mendelians knew enough mathematics to appreciate what he was doing. The biometricians were offended by Weinberg's attacks. Pearson wrote in 1909 about Weinberg's "curiously ignorant account of the biometric treatment of heredity" and said "it hardly seems needful to reply to criticisms of this character."[10] Some geneticists did not read German. Others inexplicably ignored Weinberg's work. Raymond Pearl, a Mendelian with the necessary mathematical background, had a paper published adjacent to one of Weinberg's in 1909 in *Zeitschrift für Induktive Abstammungs- und Vererbungslehre;* yet he made no reference to Weinberg's work. By the time Weinberg's efforts were appreciated, popu-

9. Wilhelm Weinberg, "Ueber Vererbungsgesetze beim Menschen. 1. Allgemeiner Teil," *Zeitschrift für Induktive Abstammungs- und Vererbungslehre*, 1 (1909): 377–92, 440–60; "Ueber Vererbungsgesetze beim Menschen. 2. Spezieller Teil," ibid., 2 (1909): 276–330; "Weitere Beiträge zur Theorie der Vererbung," *Archiv für Rassen- und Gesellschafts- Biologie* 7 (1910): 35–49, 169–73.

10. Pearson, "Darwinism, Biometry, and Some Recent Biology," p. 381.

lation genetics had already surpassed them in sophistication. Thus Weinberg had little influence upon the rise of population genetics, though he was a pioneer in the field.

THE QUANTITATIVE ANALYSIS OF INBREEDING

In the United States between 1912 and 1918 the study of the mathematical consequences of Mendelian heredity centered primarily upon the problems of inbreeding—long a subject of controversy among biologists and breeders. Some claimed inbreeding was deleterious while others claimed it was necessary to preserve desired traits in new varieties or breeds. Many geneticists realized that if a population were of known genetic composition and operated under Mendelian inheritance, one should be able to calculate the genetic composition of the population in future generations if fluctuations due to sampling were ignored. In this way the genetic consequences of inbreeding could be analyzed.

Between 1912 and 1916 H. S. Jennings and Raymond Pearl each published a series of papers on the quantitative analysis of the consequences of systems of inbreeding under Mendelian inheritance.[11] These papers attracted considerable attention and stimulated others by Wentworth and Remick[12] and Robbins.[13] The problem with all this research was the method used. The researchers assumed a certain distribution of genotypes in one generation, then laboriously calculated the distribution of genotypes in the next generation. Following this they attempted to derive by trial and error a formula for the distribution of genotypes in future generations. The method

11. H. S. Jennings, "Production of Pure Homozygotic Organisms from Heterozygotes by Self-Fertilization," *American Naturalist* 46 (1912): 487–91; "Formulae for the Results of Inbreeding," ibid., 47 (1914): 693–96; "The Numerical Results of Diverse Systems of Breeding," *Genetics* 1 (1916): 53–89. Raymond Pearl, *Modes of Research in Genetics* (New York: Macmillan, 1915), pp. 101–56. In this book Pearl summarized his research on inbreeding carried out in the years 1913–15.

12. E. N. Wentworth and B. L. Remick, "Some Breeding Properties of the Generalized Mendelian Population," *Genetics* 1 (1916): 608–16.

13. Rainard B. Robbins, "Some Applications of Mathematics to Breeding Problems," *Genetics* 2 (1917): 489–504; 3 (1918), 73–92, 375–89; "Random Mating with the Exception of Sister by Brother Mating," ibid., pp. 390–96.

worked well for simple systems of mating but became progressively cumbersome with more complex systems. Thus by 1918 the mathematical study of systems of inbreeding had reached an impasse. When the problems of inbreeding attracted the serious attention of Sewall Wright in about 1919, he abandoned the method which had led to the impasse and developed a more sophisticated method for the mathematical analysis of inbreeding. Wright's work on inbreeding was important because it deeply influenced his later mathematical analysis of evolution in nature.

THE MATHEMATICAL ANALYSIS OF SELECTION

Jennings had considered some simple cases of selection in his papers of 1916 and 1917. But a more influential account of the effects of selection in a Mendelian population had already appeared in England in 1915 in a book entitled *Mimicry in Butterflies*[14] by R. C. Punnett. His argument was that mimicry was an evolutionary phenomenon which must occur by distinct leaps: "How can we suppose that a slight variation in the direction of the model on the part of the [would-be mimic] would be of any value to it?"[15] Supposing the distinct leap were caused by a Mendelian factor, Punnett wanted to know how fast selection would cause the factor to spread through or be eliminated from the population. Accordingly, he requested the mathematician H. T. J. Norton of Trinity College, Cambridge, to prepare a table for him showing the effects of selection of various intensities acting upon a Mendelian factor in a random breeding population. Norton's table, reproduced here (see table 2), showed the number of generations required, at selection intensities of 0.50, 0.25, 0.10, and 0.01, to change the gene frequency from various intervals between 0.999 and 0.000. Punnett noted that a recessive trait with a selective disadvantage of 0.10 would be reduced in frequency from 0.44 to 0.028 in only 70 generations and that with a selective disadvantage of 0.01 the same reduction of gene frequency would require about 700 generations.

Punnett was impressed by the effectiveness of selection:

14. (Cambridge: Cambridge University Press, 1915).

15. Ibid., p. 62.

TABLE 2

Selection Table Prepared for R. C. Punnett by H. T. J. Norton

Number of generations taken to pass from one position to another as indicated in the percentages of different individuals in left-hand column												Percentage of total population formed by the new variety	Percentage of total population formed by the hybrids	Percentage of total population formed by old variety
A. Where the new variety is dominant						B. Where the new variety is recessive								
100/50	100/75	100/90	100/95	100/99	100/100	100/50	100/75	100/90	100/95	100/99	100/100			
4	10	28	300			1920	5740	17,200			189,092	·000	·09	99·9
2	5	15	165			85	250	744			8,160	·008	1·96	98·0
2	4	14	153			18	51	149			1,615	·03	9·0	90·7
2	4	12	121			5	13	36			389	2·8	27·7	69·0
2	4	12	119			2	6	16			169	11·1	44·4	44·4
4	8	18	171			2	4	11			118	25·	50·	25·
10	17	40	393			2	4	11			120	44·4	27·7	2·8
36	68	166	1,632			2	6	14			152	69·0	9·0	·03
170	333	827	8,243			2	6	16			165	90·7	1·96	·008
3840	7653	19,111	191,002			4	10	28			299	99·9	·09	·000

NOTE: Reprinted by permission of the publisher from R. C. Punnett, *Mimicry in Butterflies* (Cambridge: Cambridge University Press, 1915), p. 155.

Evolution, in so far as it consists of the supplanting of one form by another, may be a very much more rapid process than has hitherto been suspected, for natural selection, if appreciable, must be held to operate with extraordinary swiftness where it is given established variations with which to work.[16]

Norton's table also showed that selection was ineffective when acting against a rare recessive. In 1917 Punnett used this idea to discredit the claim of eugenicists that deleterious recessives could be eliminated from human populations in a few generations.[17]

Norton's table was the perfect complement to Morgan's theory of evolution by single gene replacement and it had a widespread influence. J. B. S. Haldane was stimulated by the table as was the Russian geneticist Chetverikov. Curiously, the implications of Norton's table were to undermine the discontinuous theory of evolution expounded by Punnett. The table showed clearly that small selection intensities acting for surprisingly small numbers of generations could greatly change gene frequencies in a population.

In 1917 Howard C. Warren, a Princeton psychologist, presented a short mathematical argument that Mendelism and Darwinian selection were compatible.[18] Warren treated a random breeding population for two special cases: when the dominant phenotype was twice as viable as the recessive, and when the recessive was twice as viable as the dominant. He found mathematically that selection should be effective, though the elimination was more rapid when the recessive was more viable. Warren's conclusion was that Mendelism and selection together formed a likely basis for evolutionary change. When Haldane published his first paper on mathematical selection theory in 1924 he cited Norton's table and Warren's paper as the only previous publications on the topic.

By 1918 the setting was complete for a synthesis of Mende-

16. Ibid., p. 96.

17. R. C. Punnett, "Eliminating Feeblemindedness," *Journal of Heredity* 8 (1917): 464–65.

18. Howard C. Warren, "Numerical Effects of Natural Selection Acting upon Mendelian Characters," *Genetics* 2 (1917): 305–12.

lian heredity, Darwinian selection, and biometrical methods. Mendelism was widely accepted. For explaining the success of selection acting upon small differences, Mendelism and Darwinian selection were recognized as complementary. All that remained was the quantitative synthesis with biometrical methods, some of which had already been applied to an analysis of the consequences of Mendelian heredity.

Ronald Alymer Fisher

R. A. Fisher (1890–1962) exhibited a special aptitude for mathematics and astronomy at an early age. His mother read him elementary astronomy before he was six, and several years later he was attending lectures on astronomy by Sir Robert Ball. In preparatory school teachers recognized his abilities and encouraged his mathematical investigations. While attending the Harrow School, Fisher was instructed by W. N. Roseveare, often in the evenings. Since Fisher suffered from extreme myopia and was prohibited from working by electric light, Roseveare usually taught him without visual aids—a practice that heightened Fisher's ability to visualize and solve mathematical problems in his head. Later, some mathematical statisticians and geneticists were to complain that Fisher's proofs contained intuitive leaps which were not obvious.

In 1909 Fisher entered Gonville and Caius College, Cambridge, on a scholarship. He excelled in mathematics. His tutor, the astronomer F. J. M. Stratton, encouraged him while still an undergraduate to publish a paper entitled "On an Absolute Criterion for Fitting Frequency Curves."[19] Stratton then urged Fisher to send a copy to a friend, the mathematician W. S. Gosset, who published papers under the name "Student." Gosset described his reaction to Fisher's paper in a letter to Karl Pearson on 12 September 1912:

> Stratton, the tutor, made him [Fisher] send me [the paper] and with some exertion I mastered it, spotted the fallacy (as I believe) and wrote him a letter showing, I hope, an intelligent interest in the matter and incidentally making a blunder. To this he replied with two foolscap pages covered with mathematics of the deepest dye in which he proved [what he had previously claimed] and of course exposed my mistake. I couldn't understand his stuff and wrote and said I was going to study it when I had time.[20]

19. *Messenger of Mathematics* 41 (1912): 155–60.

Despite Gosset's less than encouraging reply, Fisher wished to continue corresponding with him because they were interested in similar mathematical investigations. In 1908 Gosset had published without proof the exact solution for the test of the significance of the mean of a small sample of normally distributed material. Fisher took up the problem and by early September 1912 he had derived a rigorous proof of Gosset's solution. He sent his calculations to Gosset, who again could not understand them. Gosset sent Fisher's proof on to Pearson with the comment, "it seems to me that if it's all right perhaps you might like to put the proof in a note [in *Biometrika*]. It's so nice and mathematical that it might appeal to some people."[21] Clearly by 1912, at age twenty-two, Fisher was already an accomplished mathematician.

While at Cambridge, Fisher's interests were not confined to pure mathematics. He discovered Karl Pearson's series "Mathematical Contributions to the Theory of Evolution" and became interested in genetics and evolution. The Mendelians were influential at Cambridge and Fisher, unlike Pearson, soon became convinced that Mendelism was the prevailing mechanism of heredity. He also studied astronomy at Cambridge. After graduating in 1912 he stayed for another year with a studentship in physics, studying under James Jeans and his former tutor Stratton. In the years following his departure from Cambridge in 1913, Fisher's primary interests were in the fields of mathematical statistics and evolutionary theory.

For several years before 1914, Pearson and his colleagues had been concerned with the reliability of a correlation coefficient derived from a sample of a much larger population. In September 1914, Fisher solved the problem by deriving the exact

20. W. S. Gosset to Karl Pearson, 12 September 1912. Reprinted in E. S. Pearson, "Studies in the History of Probability and Statistics. 20. Some Early Correspondence between W. S. Gosset, R. A. Fisher, and Karl Pearson, with Notes and Comments," *Biometrika* 55 (1968): 446.

21. Ibid.

distribution of the values of the correlation coefficient in samples from an indefinitely large population. He sent the derivation to Pearson who wrote back on 26 September 1914 to say "I congratulate you very heartily on getting out the exact distribution form of r. . . . If the analysis is correct which seems highly probable, I should be delighted to publish the paper in *Biometrika*." [22]

Fisher's derivation of the exact distribution of the correlation coefficient was of little value in practical usage without the computation of tables of the distribution of r for various sample sizes. Thus even before the appearance of Fisher's paper in *Biometrika* in May 1915 both Fisher and Pearson (with the resources of his statistical laboratory) were working on tables for the distribution of r. Unfortunately the war prevented easy communication between Fisher and the workers at Pearson's statistical laboratory. The breakdown in communications allowed Pearson's group to proceed without understanding some parts of Fisher's 1915 paper and caused Fisher some unnecessary work. Relations between the two men began to be strained. On 15 May 1916 Fisher wrote Pearson that "I could probably have worked more profitably, if I had been in closer touch with the Laboratory, although such collaboration is never easy." [23]

The May 1916 issue of *Biometrika* contained a paper by Kirstine Smith on the "best" values of the constants in frequency distributions. Fisher disagreed with her conclusions and immediately wrote a note of rebuttal which he submitted to Pearson for publication in *Biometrika*. In the same letter with the note he informed Pearson: "I have recently completed an article on Mendelism and Biometry which will probably be of interest to you. I find on analysis that the human data is as far as it goes, not inconsistent with Mendelism. But the argument is rather complex." [24] Pearson replied on 26 June that he disagreed with Fisher's criticism of Miss Smith and declined to publish the note.[25] From his experience with the Mendelians Pearson understandably wanted to avoid controversies. In his reply he did not mention Fisher's paper on Mendelism and biometry, but he cannot have agreed with Fisher's thesis. When Fisher's paper was finally published in October 1918, he immediately sent Pearson a copy and received this reply: "Many thanks for your memoir which I hope to find time for. I am afraid I am not a believer in cumulative Mendelian factors as being the solution of the heredity puzzle." [26] Thus Pearson flatly rejected Fisher's thesis even before reading the paper. After 1918 the complications arising from the disagreements between Fisher and Pearson strained relations between them beyond repair.

22. Pearson to Fisher, ibid., p. 448.
23. Fisher to Pearson, ibid., p. 451.
24. Ibid., p. 454.
25. Pearson to Fisher, ibid., p. 455.

Fisher's approach to Mendelism and biometry was that advocated by Yule more than ten years earlier. He wanted to synthesize Darwinism, Mendelism, and biometry. Probably by 1912 Darwin's *Origin of Species* and Pearson's papers had convinced Fisher that natural selection was the primary agent of evolutionary change and that it operated upon apparently continuous variations. In this sense Fisher was a firm Darwinian. But he disagreed with Pearson's and Darwin's analysis of continuous variation. Pearson claimed, and Darwin would probably have agreed, that the continuous variations in a pure line were heritable and that continued selection in a pure line should be effective. Because blending inheritance eliminated much of the heritable variation each generation Darwin believed that many new continuous variations must be heritable. Otherwise the supply of heritable variation in a population would be drastically depleted within a few generations. Probably as a result of the influence of the Cambridge Mendelians, Fisher, unlike Pearson, believed in Mendelian inheritance and the continuity of the germ plasm. He quickly realized, along with Bateson, de Vries, and others, that individual factors were not blended away by crossing. He saw that the mathematical consequences of Mendelian heredity in general preserved Mendelian factors, and thus heritable variability, in the population. He knew that selection in a pure line with genetically identical individuals must be ineffective. It followed that much

of the continuous variation in a heterogeneous population where selection was effective must be capable of explanation in Mendelian terms. Fisher set out to demonstrate what Yule had suggested and Weinberg proved in some detail: that Mendelism could account for observed correlations between relatives, despite Pearson's belief to the contrary. He apparently was unaware of Weinberg's work.

Fisher completed his paper on Mendelism and biometry by June 1916 and submitted the paper to the Royal Society of London for publication. The referees suggested it be withdrawn. He subsequently submitted the paper to the Royal Society of Edinburgh, which with his financial assistance published it on 1 October 1918 under the title "The Correlation between Relatives on the Supposition of Mendelian Inheritance."[27]

Fisher's express purpose in the paper was to interpret the well-established results of biometry in terms of Mendelian inheritance by ascertaining the biometrical properties of a Mendelian population. In particular, he wanted to show that Pearson was mistaken in concluding that the correlations between relatives in man contradicted the Mendelian scheme of inheritance. He began by defining a measure of the variability of a character in a population. Often the standard deviation σ was utilized for this purpose. But Fisher noted that

> when there are two independent causes of variability capable of producing in an otherwise uniform population distributions with standard deviations σ_1 and σ_2, it is found that the distribution, when both causes act together, has a standard deviation $\sigma_1^2 + \sigma_2^2$. It is therefore desirable in analysing the causes of variability to deal with the square of the standard deviation as the measure of variability. We shall term this quantity the Variance of the normal population to which it refers, and we may now ascribe to the constituent causes fractions or percentages of the total variance which they together produce.[28]

The paper was devoted to an analysis of the constituent parts of the total variance in a Mendelian population.

27. *Transactions of the Royal Society of Edinburgh* 52 (1918): 399–433.

28. Ibid., p. 399.

He pointed out that the observed correlation between relatives was an unreliable direct measure of the percentage of the total variance contributed by ancestors:

> For stature the coefficient of correlation between brothers is about .54, which we may interpret by saying that 54 per cent of their variance is accounted for by ancestry alone, and that 46 per cent must have some other explanation.
>
> It is not sufficient to ascribe this last residue to the effects of environment. Numerous investigations by Galton and Pearson have shown that all measurable environment has much less effect on such measurements as stature. Further, the facts collected by Galton respecting identical twins show that in this case, where the essential nature is the same, the variance is far less. The simplest hypothesis, and the one which we shall examine, is that such features as stature are determined by a large number of Mendelian factors, and that the large variance among children of the same parents is due to the segregation of those factors in respect to which the parents are heterozygous. Upon this hypothesis we will attempt to determine how much more of the variance, in different measurable features, beyond that which is indicated by the fraternal correlation, is due to innate and heritable factors.[29]

Fisher knew that some influences tended to obscure the actual genetic similarity between relatives. Dominance could cause different somatic effects with identical genetic changes. Genic interaction, or epistasis, could also cause this. Fisher termed these genetic processes "nonadditive." Thus he divided the total genetic contribution from one generation to another into an additive part and a nonadditive residue.

From the pure line work it was obvious that environmental influences also tended to obscure the actual genetic similarity between relatives. In 1906 Yule had suggested that the effects of incomplete dominance and the environment, when taken into account, would show that Mendelian heredity and observed correlations between human relatives were compatible. Pearson had claimed they were incompatible. Yule also made the comment that "so far as the coefficients of correlation alone are concerned, it is . . . impossible to distinguish between the effects of the heterozygote giving rise to forms that are not

29. Ibid., p. 400.

strictly intermediate, and the effect of the environment in causing somatic variations which are not heritable." [30] In other words, it was impossible to distinguish the effects of environment from the effects of dominance in the correlations between relatives. Fisher showed that Yule was wrong; these effects could be distinguished.

It was well known by the biometricians that fraternal correlation usually exceeded parental. Noting that the variance in a sibship, apart from environmental effects, depended only upon the number of factors in which the parents are heterozygous, Fisher calculated the fraternal correlation as compared to parental correlation. The calculation showed that

> the effect of dominance is to reduce the fraternal correlation to only half the extent to which the parental correlation is reduced. This allows us to distinguish, as far as the accuracy of the existing figures allows, between the random external effects of environment and those of dominance.[31]

By analyzing the extent to which fraternal correlation exceeded parental, he was able to distinguish the contributions of dominance and environment to the total variance.

In addition to accounting for the effects of dominance, Fisher examined the statistical consequences of genic interaction, assortative mating, multiple alleles, and linkage upon the correlations between relatives. He believed the effects of genic interaction and linkage were negligible in a large population. He extended his analysis to the correlations between uncles and cousins and other relatives. Then, using the data of Pearson and Lee on man,[32] from which Pearson had concluded the inadequacy of Mendelian inheritance, Fisher demonstrated that "the hypothesis of cumulative Mendelian factors seems to fit the facts very accurately." [33] One important conclusion he made from the application of his theory to the data of Pearson and Lee was that "it is very unlikely that so much

30. Yule, "On the Theory of Inheritance," p. 142.
31. Fisher, "The Correlations between Relatives," p. 406.
32. Karl Pearson and Alice Lee, "On the Laws of Inheritance in Man. I. Inheritance of Physical Characters," *Biometrika* 2 (1903): 357–462.
33. Fisher, "The Correlations between Relatives," p. 433.

as 5 per cent of the total variance is due to causes not heritable." [34] Fisher concluded that many continuously varying characters such as human stature were primarily determined by many Mendelian factors not environmental influences.

Fisher's 1918 paper was well received by the few geneticists who could understand his mathematics. Encouraged, he next attempted the task from which William Bateson had shrunk: to quantitatively examine the evolutionary consequences of Mendelian heredity. In 1922 he published a substantial paper on this topic.[35] He discussed the interaction of selection, dominance, mutation, random extinction of genes, and assortative mating. The germinal ideas of many of his later researches into evolution were contained in this paper. First he treated the problem of equilibrium under selection. For a single locus with two alleles, he showed that if selection favored one homozygote the other allele would be eliminated. He then stated the possibility of a balanced polymorphism and its consequences:

> If, on the other hand, the selection favors the heterozygote, there is a condition of stable equilibrium, and the factor will continue in the stock. Such factors should therefore be commonly found, and may explain instances of heterozygote vigor, and to some extent the deleterious effects sometimes brought about by inbreeding.[36]

Next he considered the problem of the survival of individual genes. He found that individually a gene had a very small chance of surviving. The survival of a rare gene depended upon chance rather than selection. A mutation would be more likely to become fixed at low frequencies in a large instead of a small population simply because the mutation would more often survive in a large population. "Thus a numerous species, with the same frequency of mutation, will maintain a higher variability than will a less numerous species: in connection with this fact we cannot fail to remember the dictum of Charles Darwin that 'wide ranging, much diffused and com-

34. Ibid., p. 524.
35. R. A. Fisher, "On the Dominance Ratio," *Proceedings of the Royal Society of Edinburgh* 42 (1922): 321–41.
36. Ibid., p. 324.

mon species vary most.'"[37] A consequence of this point of view was that a smaller mutation rate could balance the effects of adverse selection in a large population more easily than in a small population. This idea was a fundamental tenet of Fisher's view of evolution.

In 1921 A. L. and A. C. Hagedoorn had published the theory that the random survival of genes in populations was more important than preferential survival as a result of selection.[38] Attacking this idea with vigor, Fisher demonstrated that even with the absence of new mutations in a population of moderate size (about 10,000 individuals) the rate of gene extinction was exceedingly small. He therefore rejected the importance of the chance elimination of genes as compared with the elimination by selection.

If the heterozygote were intermediate between the homozygotes at a locus, Fisher showed that selection could quickly eliminate one allele. But in the case of complete dominance, selection was ineffective in removing deleterious recessives present at low frequencies. Thus under the protection of dominance there was an accumulation of rare recessives in the population. This effect was heightened in large populations because a low frequency of mutation could sustain the presence of an allele.

In the 1918 paper Fisher defined the quantity α^2 as the contribution which a single locus makes to the total variance.[39] He now concluded on the basis of his calculations that one

effect of selection is to remove preferentially those factors for which α is high, and to leave a predominating number in which α is low. In any factor α may be low for one of two reasons: (1) the effect of the factor on development may be very slight, or (2) the factor may effect changes of little adaptive importance. It is therefore to be expected that the large and easily recognised factors in natural organisms will be of little adaptive importance, and that the factors affecting important adaptations will be individually of very slight effect. We should thus expect that variation in organs of adaptive

37. Ibid.

38. A. L. and A. C. Hagedoorn, *The Relative Value of the Processes Causing Evolution* (The Hague: Martinus Nyhoff, 1921).

39. Fisher, "The Correlations between Relatives," p. 402.

importance should be due to numerous factors, which individually are difficult to detect.[40]

Fisher's basic ideas concerning the process of evolution were expressed in this paper. He believed, in accordance with his biometrical training, that evolution was primarily concerned with large populations where variability, because of storage of genes, was high. In such populations the deterministic results of selection acting upon single gene effects reigned supreme. Natural selection was slow but sure. Fisher even went so far as to compare the rules governing evolutionary change to the general laws of the behavior of gases. The investigation of natural selection

may be compared to the analytic treatment of the Theory of Gases, in which it is possible to make the most varied assumptions as to the accidental circumstances, and even the essential nature of the individual molecules, and yet to develop the general laws as to the behavior of gases, leaving but a few fundamental constants to be determined by experiment.[41]

Among the negligible "assumptions as to the accidental circumstances" in evolutionary theory were the effects of genic interaction and random genetic drift. Sewall Wright was to disagree with Fisher's judgment in these cases. Fisher's theory of evolution, like Morgan's, was based upon single gene replacements. Fisher, however, emphasized the smallness of the variations and the slowness of natural selection far more than Morgan, who thought in terms of sizable mutations and relatively rapid selection.

Between 1922 and 1929 Fisher published a series of papers amplifying or experimentally verifying aspects of the evolutionary view presented in his 1922 paper. In 1926 he and E. B. Ford published a study of thirty-five species of British moths.[42] They found, in accordance with Fisher's 1922 prediction, that in one locality the abundant species exhibited much more variability than the rare species with respect to a continuously vari-

40. Fisher, "On the Dominance Ratio," p. 334.

41. Ibid., pp. 321–22.

42. R. A. Fisher and E. B. Ford, "Variability of Species," *Nature* 118 (1926): 515–16.

able character. Fisher considered this data an excellent verification of his theory.

Fisher's theory of evolution harmonized with Darwinian evolution rather than discontinuous evolution. In 1927 one last bastion of the adherents of discontinuous evolution was mimicry theory. In England R. C. Punnett was the champion of discontinuous evolution in mimicry. His 1915 book *Mimicry in Butterflies* was widely read by entymologists. Punnett's theory of mimicry was distasteful to Fisher because it exemplified, he felt, the wrong application of Mendelism to discontinuous evolution. On 5 October 1927 Fisher read a paper before the Entymological Society of London in which he attacked discontinuous evolution in mimicry. In the introduction he stated the general problem:

> It is now becoming increasingly widely understood that the bearing of genetical discoveries, and in particular of the Mendelian scheme of inheritance, upon evolutionary theory is quite other than that which the pioneers of Mendelism originally took it to be. These were already, at the time of the rediscovery of Mendel's work, in the full current of that movement of evolutionary thought, which in the nineties of the last century, had set in favour of discontinuous origin for specific forms. It was natural enough, therefore, that the discontinuous elements in Mendelism should, without sufficiently critical scrutiny, have been interpreted as affording decisive evidence in favour of this view. . . . It should be borne in mind that the reinterpretation of the significance of Mendelism in cases of mimicry is but part of a more general recovery of genetical opinion from positions adopted at a somewhat immature stage of the development of that science.[43]

In the body of the article Fisher first carefully examined the foundation of mimicry theory, especially the ideas of Henry Bates and Fritz Müller and the revisions suggested by G.A.K. Marshall, and then Punnett's theory. Punnett's proof of discontinuity seemed convincing. He had found (in 1915) that the differences among three forms of the butterfly *Papilio polytes* in Ceylon were caused by an apparently stable polymorphism involving two Mendelian factors, one of which was necessary for the manifestation of the second. The differences among the three forms were clearly discontinuous; so, in Punnett's view, the forms must have originated by discontinuous leaps.

43. R. A. Fisher, "On Some Objections to Mimicry Theory; Statistical and Genetic," *Transactions of the Entymological Society of London* 75 (1927): 269.

Punnett assumed without mention that the phenotypic manifestation of the Mendelian factors involved had always been the same. Fisher challenged this assumption. Citing Castle's experiments in which the expression of the factor for the hooded pattern in rats had been significantly changed by the accumulation of modifiers, he suggested that a similar accumulation of modifiers could have changed the expression of the factors involved in the polymorphism in *Papilio polytes*. Generally, in a population where a stable polymorphism existed, if "selection favours different modifications of the two genotypes, it may become adaptively dimorphic by the cumulative selection of modifying factors, without alteration of the single-factor mechanism by which the polymorphism is maintained."[44] Thus Fisher provided a theory of mimicry based upon the deterministic effect of selection acting upon small modifiers. In so doing he helped bring down the last major stronghold of some Mendelians who advocated the discontinuous, anti-Darwinian theory of evolution.

The phenomenon of dominance had long troubled geneticists. Not only was the physiological mechanism of dominance obscure, but also the mechanism of the evolution of dominance was unclear. Fisher became interested in these problems and in 1928 he published a theory of the evolution of dominance.[45] The theory was based upon his conviction that the populations important in evolution were large and that very small selection pressures exerted over long periods of time were crucial in species change. He argued that most mutations tended to be deleterious and to occur at a finite rate. Thus in a large population over a long period of time a mutant

allele was likely to become fixd at low frequencies in the population. Selection against the mutant allele would be balanced by recurrent mutation. Initially, the heterozygote between the new mutant allele and the wild type allele would be intermediate between the homozygous types, in expression and fitness. Since the heterozygotes would be much more frequent in the population than the mutant homozygotes, selection would tend to preserve those heterozygotes which, because of modifying factors, more closely resembled the homozygous wild type. By selection of modifier factors the heterozygote would eventually become phenotypically indistinguishable from the wild type, thus accomplishing dominance. The selection pressures acting upon the modifiers were small, of the order of mutation rates, but Fisher believed such selection pressures were effective given enough time. Both Wright and Haldane disagreed with Fisher's theory of the evolution of dominance, and this disagreement illuminates the way all three differed in their ideas of evolution.

By 1929 Fisher believed he had worked out a relatively complete theory of evolution, synthesizing Mendelian inheritance and Darwinian selection. He put forth his theory in *The Genetical Theory of Natural Selection,*[46] published in 1930. He later stated that one reason he wrote the book was "to demonstrate how little basis there was for the opinion . . . that the discovery of Mendel's laws of inheritance was unfavorable, or even fatal, to the theory of natural selection."[47] In the first chapter Fisher demonstrated mathematically that the consequence of Darwin's assumption of blending inheritance was that "the heritable variance is approximately halved in every generation."[48] Thus Darwin's theory required the appearance of an enormous amount of new variation each generation. Fisher showed that Mendelian inheritance offered a solution to this problem in Darwin's theory because it conserved the variance in the population. In this chapter he also challenged

46. (Oxford: Clarendon Press, 1930).
47. R. A. Fisher, "Retrospect of the Criticisms of the Theory of Natural Selection," *Evolution as a Process,* ed. Julian Huxley, A. C. Hardy, and E. B. Ford (New York: Collier Books, 1963), p. 104.
48. Fisher, *The Genetical Theory of Natural Selection,* p. 5.

the argument used by de Vries, Bateson, Punnett, and many others that small heritable variations could have no selective advantage. Fisher argued that

> if a change of 1mm. has selection value, a change of 0.1 mm. will usually have a selection value approximately one-tenth as great, and the change cannot be ignored because we deem it inappreciable. The rate at which a mutation increases in numbers at the expense of its allelomorph will indeed depend upon the selective advantage it confers, but the rate at which a species responds to selection in favour of any increase or decrease of parts depends on the total heritable variance available, and not on whether this is supplied by large or small mutations.[49]

The second chapter introduced Fisher's "fundamental theorem of natural selection." The basic idea was that the effectiveness of selection depended upon the total heritable variance available in the population at that time. If fitness were measured by the ability of a gene to survive and be represented in future generations, then natural selection tended to increase the total fitness of the population. The rate of increase in fitness depended upon the amount of genetic variance in fitness available. Fisher derived his fundamental theorem mathematically, then stated it in words as: *"The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time."*[50] He compared this general formulation of the action of natural selection not only with the gas laws but also with the second law of thermodynamics. A population always increased in fitness according to Fisher's fundamental theorem, but the process could be continued indefinitely because of the deterioration of the environment, such as increase in mutagens, changes in the physical environment, or increase of the population causing more intense intraspecific competition.

The next five chapters of Fisher's book were devoted to restatement and expansion of views he had expressed in his earlier papers. In the concluding five chapters he extended his

49. Ibid., pp. 15–16.
50. Ibid., p. 35.

genetical ideas to human populations. In 1930 the *Genetical Theory of Natural Selection* represented the most substantial contribution to the synthesis of Mendelism, Darwinism, and biometry yet published.

Sewall Wright

Sewall Wright approached the problem of evolution with a background different from Fisher's.[51] His interest in evolution was spurred by reading Vernon L. Kellogg's *Darwinism Today*[52] when he was an undergraduate at Lombard College in Galesburg, Illinois. Unlike Fisher, his formal mathematical training was sparse, extending only so far as elementary differential and integral calculus, although he later taught himself a great deal of mathematics as the necessity arose in his quantitative work on evolution. He went to the University of Illinois in 1911 for graduate study in biology. During that year William Castle, then at the Bussey Institution of Harvard, came to give a talk on genetics. Wright was fascinated with his ideas. Since there was no opportunity at this time for him to study genetics at Illinois, Castle encouraged him to transfer to the Bussey Institution. Wright did so the following year and remained there for the years 1912–15.

His work in Castle's laboratory centered upon physiological genetics. He conducted an extensive study of the inheritance of color and other coat characters in guinea pigs and found that the inheritance of color was controlled by an interaction system of genes.[53] This result was important in the development of Wright's later thought on selection and evolution. He was convinced that interaction systems of genes were important in the life of organisms. Thus what was important in evolution was the fate of interaction systems, not just single genes. From the beginning of his work in genetics Wright was

51. I am indebted to Sewall Wright for allowing me two lengthy interviews. His comments elucidated not only his own development but also the work of Fisher, Haldane, and many others.

52. (New York: Henry Holt, 1907).

53. Sewall Wright, *An Intensive Study of the Inheritance of Color and of Other Coat Characters in Guinea-Pigs, with Especial Reference to Graded Variations,* Carnegie Institution of Washington Publication, no. 241 (Washington, D.C., 1916), pp. 59–60.

more concerned with interaction effects than Fisher or Haldane.

While at the Bussey Institution, Wright also helped Castle with the selection experiment on hooded rats. He was fully convinced of the effectiveness of selection in altering a character beyond its former limits of variation. The crucial experiment which demonstrated conclusively that Castle had been selecting modifying factors rather than a single varying factor was suggested by Wright.

Wright had only one brush with population genetics while at the Bussey Institution. In 1913 Raymond Pearl published his first paper on the mathematical consequences of inbreeding in a Mendelian population. He claimed that there was absolutely no "automatic increase in the proportion of homozygotes necessarily following any other sort of inbreeding except self-fertilization"[54] and tried to demonstrate that continued brother-sister mating caused no increase in the proportion of homozygotes. H. D. Fish, a student in the same laboratory as Wright, saw (along with others) that Pearl must be wrong. But Fish knew little mathematics and covered a huge number of scratch pages with calculations without disproving Pearl's assertions. Finally he so cluttered up the laboratory with his pages of calculations that Wright felt compelled to help him. Wright quickly worked out a formula for calculating the composition of the population at any generation, which Fish used to show that continued brother-sister mating indeed caused the population to become progressively more homozygous. Much to Pearl's chagrin, Fish then published his results.[55] Wright participated in this little adventure simply for diversion. At the time he had no inkling that six years later he would devise a powerful general method for the analysis of the consequences of inbreeding in Mendelian populations.

In 1915 Wright left the Bussey Institution for the Animal Husbandry Divison of the United States Department of Agri-

54. Raymond Pearl, "A Contribution towards an Analysis of the Problem of Inbreeding," *American Naturalist* 47 (1913): 606.

55. Fish published his figures as a note in an article by Phineas T. Whiting, "Heredity of Bristles in the Common Greenbottle Fly," *American Naturalist* 48 (1914): 343–44.

culture, where he continued work on genetic interaction systems affecting color inheritance. During 1917 and 1918 he published eleven papers on color inheritance in mammals. In addition to elucidating the interaction systems in color inheritance, Wright in these papers also used the Hardy-Weinberg equilibrium principle to calculate genotype frequencies in populations as a means of discriminating between genetical hypotheses.[56] At the time Wright wrote these papers he was not acquainted with the genetical work of Hardy or Weinberg. But the equilibrium principle which later carried both their names seemed intuitively obvious to Wright, and he referred to it as "the well known formula for a Mendelian population in equilibrium." [57]

At the Animal Husbandry Division, Wright also assumed charge of an extensive inbreeding experiment on guinea pigs begun in 1906 by G. M. Rommel. Faced with the task of analyzing the accumulated data, he became seriously interested in constructing a general mathematical theory of inbreeding. Seeing that the method previously utilized by Pearl, Jennings, Wentworth and Remick, and Robbins was too cumbersome with complex systems of mating, he searched for a new way to approach the problem of inbreeding. In 1920 he discovered that his method of path coefficients, which he had previously developed for other reasons, provided the powerful tool he needed for the analysis of systems of breeding in general.

Wright first used the mehod of path coefficients, although he did not use that terminology, in a paper in 1917 with the title "On the Nature of Size Factors." [58] In 1914, Castle had published a short paper on the correlations between five bone measurements in a stock of rabbits. He found that the correlations were "all positive and fairly high. . . . In view of the high correlations obtaining between one skeletal dimension and another . . . it follows that to a large extent the

56. Using the equilibrium principle Wright distinguished between a one-factor and a two-factor hypothesis in the coat color of cattle in "Color Inheritance in Mammals. 6. Cattle," *Journal of Heredity* 8 (1917): 521–27. He also showed that eye color in humans did not depend upon single factor inheritance in "Color Inheritance in Mammals. 11. Man," ibid., 9 (1918): 231–32.

57. Wright, "Color Inheritance in Mammals. 6. Cattle," p. 522.

factors which determine size are *general* factors affecting all parts of the skeleton simultaneously." [59] Wright helped compute the correlation tables for Castle's paper. Then in 1917 Charles B. Davenport published a long paper on the inheritance of stature in man.[60] He claimed that size factors which affected only particular segments of stature were more important than factors which affected the growth of the body as a whole. Wright decided to reevaluate Castle's data in the light of Davenport's contentions. In his paper Wright proposed "to illustrate a method of analysis as well as to bring out certain conclusions." [61]

Wright's method was designed to estimate the degree to which a given effect was determined by each of a number of causes. In this case he treated the causes, namely, factors which affected general size and factors which affected separate parts, as independent. Wright's first formulation of the theory of path coefficients was as follows:

> Let X and Y be two characters whose variations are determined in part by certain causes A, B, C, etc., which act on both and in part by causes which apply to only one or the other, M and N respectively. These causes are assumed to be independent of each other. Represent by small letters a, b, c, etc., the proportions of the variation of X determined by these causes and by a^1, b^1, c^1, etc., the proportions in the case of Y. The extent to which a cause determines the variation in an effect is measured by the proportion of the squared standard deviation of the latter for which it is responsible. This follows from the proposition that the squared standard deviations due to single causes acting alone may be combined by simple addition to find the squared standard deviation of an array in which all causes are acting, provided the causes are independent of each other. . . . As a, b, etc., are the proportions of the variation of X which are determined by the various causes
>
> $$[\mathrm{I}] \quad \begin{matrix} a+b+c+d \ \ldots\ldots\ldots\ldots + m = 1 \\ a^1+b^1+c^1+d^1 \ \ldots\ldots\ldots + n^1 = 1 \end{matrix}$$

59. W. E. Castle, *The Nature of Size Factors as Indicated by a Study of Correlation*, Carnegie Institution of Washington Publication, no. 196 (Washington, D.C., 1914), p. 51.

60. Charles B. Davenport, "Inheritance of Stature," *Genetics* 2 (1917): 313–89.

It is easy to demonstrate the following proposition in regard to the correlation between X and Y.

$$[\text{II}] \quad r_{xy} = \pm\sqrt{aa^1} \pm \sqrt{bb^1} \pm \sqrt{cc^1} \ldots .^{62}$$

By making the sums of the degrees of determination equal to unity (equations I) and expressing the known correlation in terms of the unknown degrees of determination (equation II), a series of simultaneous equations were formed and could be solved for the unknown effects of single causes. In the case of size factors in rabbits, Wright's model showed that "most differences between individuals are those which involve the size of the body as a whole." [63]

Wright soon found another application for his new method. He had observed that even after twenty generations of intense inbreeding a family of guinea pigs with a tricolor coat might yield offspring with very different amounts of each color. But because of the intense inbreeding the family should be nearly homozygous. Wright suspected that the variations in coat color were caused by environmental factors. He wanted a method to measure the relative importance of heredity and environmental factors which he could apply to the case of coat color in his stocks of guinea pigs.

Wright's paper on this topic was published in 1920. He began by defining a path coefficient as "the ratio of the variability of the effect to be found when all causes are constant except the one in question, the variability of which is kept unchanged, to the total variability. Variability is measured by the standard deviation." [64] In the earlier paper the proportions of variation in a character determined by causes *A, B, C,* etc., and denoted by *a, b, c,* etc., were the squares of the respective path coefficients. Wright extended his theoretical model to include a simple case where the causes were correlated instead of independent. He then applied the method of path coefficients to the problem of ascertaining the relative importance of

62. Ibid., pp. 370–71.
63. Ibid., pp. 373–74.
64. Sewall Wright, "The Relative Importance of Heredity and Environment in Determining the Piebald Pattern of Guinea-Pigs," *Proceedings of the National Academy of Sciences* 6 (1920): 329.

heredity and environment in determining the piebald pattern in guinea pigs. He found that in the highly inbred stocks heredity determined almost none of the variability and irregularity in development determined almost all of it. This was of course the expected result because the inbred stock was probably very nearly homozygous.

In January 1921 Wright published, under the title "Correlation and Causation," [65] his general theory of path coefficients. He was now able to treat systems of independent and correlated causes, nonadditive factors, and nonlinear relations. He derived a general formula for the expression of the correlation between any two variables in terms of path coefficients: "the correlation between two variables is equal to the sum of the products of the chains of path coefficients along all of the paths by which they are connected." [66] In this paper he applied the method to factors which determined birth weight in guinea pigs and to factors which affected the rate of transpiration in plants. Wright was aware of the flexibility of his method of path coefficients and he applied it in many ways during the next ten years.

Perhaps the most striking application of the method of path coefficients was to the effects of various systems of mating. Under the general heading of "Systems of Mating," [67] Wright published in 1921 a series of five papers in which he explored the biometric relation between parent and offspring, the effects of various systems of inbreeding on the genetic composition of a population, the effects of assortative mating, and the effects of selection. The method of path coefficients was much easier to apply to the problems of inbreeding than the direct method utilized by earlier workers. Wright was able to quickly corroborate earlier researches and then extend his method to systems of mating for which the direct method was far too cumbersome. The method provided an easy way to calculate the increase in the percentage of homozygosis in successive generations under various systems of inbreeding. In

65. *Journal of Agricultural Research* 20 (1921): 557–85.
66. Ibid., p. 568.
67. Sewall Wright, "Systems of Mating," *Genetics* 6 (1921): 111–78.

the years 1923–26 Wright also used the theory of path coefficients to analyse the history of inbreeding in the development of shorthorn cattle.

Having developed a general theory of the quantitative consequences of inbreeding, Wright was now prepared to analyze in depth the extensive results of the inbreeding experiments with guinea pigs which had continued under his direction since 1915.[68] Wright's conclusions about these inbreeding experiments are crucial to an understanding of his later views on the process of evolution. The data showed that the brother-sister mating was carried on for over twenty generations in many of the families, and a control stock was maintained. The highly inbred stocks exhibited a general decline in all elements of vigor, including mortality at birth and between birth and weaning, the size of litter, the weight at various ages, the regularity in producing litters, and the resistance to tuberculosis. Several families, however, despite intense inbreeding, exhibited no obvious degeneration.

One important effect of continued intense inbreeding was differentiation among the families. Fixation of many combinations of color, number of toes, elements of vigor, and various abnormalities occurred in each inbred family. When highly inbred stocks with fixed heritable characters were crossed there was a marked recovery of the vigor exhibited by the control stock.

Wright interpreted the results of the inbreeding experiments in accordance with the theories of East and Jones:[69]

> The fundamental effect of inbreeding is the automatic increase in homozygosis in all respects. An average decline in vigor is the consequence of the observed fact that recessive factors, more extensively brought into expression by an increase in homozygosis, are more likely to be deleterious than are their dominant allelomorphs. The differentiation among the families is due to the chance fixation of different combinations of the factors present in the original heterozygous stock. Crossing results in improvement because each family in general supplies some dominant factors lacking in the others.[70]

68. Sewall Wright, "The Effects of Inbreeding and Crossbreeding on Guinea Pigs," *Bulletin of the U.S. Department of Agriculture,* nos. 1090 and 1121 (1922).

69. See Edward M. East and Donald F. Jones, *Inbreeding and Outbreeding* (Philadelphia: J. B. Lippincott, 1919).

Wright suggested a theory, based upon the experimental results obtained with guinea pigs, of how to combine inbreeding, crossbreeding, and selection for the most effective improvement of livestock. The characteristics he had studied in guinea pigs,

> like most of those of economic importance with livestock, are of a kind which is determined only to a slight extent by heredity in the individual. . . . Progress by ordinary selection of individuals would thus be very slow or nil. A single unfortunate selection of a sire, good as an individual, but inferior in heredity, is likely at any time to undo all past progress. On the other hand, by starting a large number of inbred lines, important hereditary differences in these respects are brought clearly to light and fixed. Crosses among these lines ought to give a full recovery of whatever vigor has been lost by inbreeding, and particular crosses may safely be expected to show a combination of desired characters distinctly superior to the original stock. Thus a crossbred stock can be developed which can be maintained at a higher level than the original stock, a level which could not have been reached by selection alone.[71]

Wright was convinced by ten years of experimental work that interaction systems of genes were an important part of the genetic constitution of organisms. The advantage of his theory of artificial selection was that whole interaction systems would be fixed by inbreeding and could then be selected. Selection, instead of operating upon single gene effects, could operate upon entire interaction systems. Wright believed that simple direct selection for single gene effects was far less effective than the selection of interaction systems.

He soon began to apply his conclusions about effective livestock breeding to the problem of evolution in nature. By 1925, when he left the Animal Husbandry Division for a

70. Wright, "Effects of Inbreeding and Crossbreeding on Guinea Pigs," no. 1121, pp. 48–49.

71. Ibid., p. 49.

position at the University of Chicago, Wright had written a long paper on evolution. He was dissatisfied with some of his mathematical calculations and withheld the paper from publication until 1931, but his general approach to the problem of evolution was clear in his mind by 1925.

Wright was convinced from his experimental work that interaction systems were important in evolution and that the random drift of genes caused by inbreeding was important for the creation of novel interaction systems. His theory of evolution was constructed with these ideas in mind. Thus from the beginning of his work on evolution Wright differed markedly from Fisher, who denied the importance of genic interaction and random genetic drift in evolution. Fisher believed that natural selection operated most effectively in large populations, because more variant genes were stored there. Natural selection, as stated by his fundamental theorem, acted to increase the fitness of a single interaction system by single gene replacements. Wright on the other hand believed that natural selection operated most effectively in smaller populations where inbreeding was sufficiently intense to create new interaction systems through random drift but not intense enough to cause random nonadaptive fixation of genes. Natural selection could then act upon the new interaction systems. In this way the population could change much more rapidly than by mass selection of single genes.

Wright disagreed with Fisher's theory of dominance. In his first paper on dominance Fisher had stated "that with mutation rates of one in a million the corresponding selection in the state of nature, though extremely slow, can not safely be neglected in the case of the heterozygotes." [72] Using Fisher's hypothesis, Wright calculated the selection pressures operating upon modifiers of dominance in heterozygotes and found they were of the order of mutation rates. Because of his strong belief in the universality of genic interaction, he doubted that such small selection pressures were important in the fixation of modifiers of dominance: "It has been shown

72. Fisher, "Possible Modification of the Response of the Wild Type to Recurrent Mutations," p. 126.

that genes often have multiple effects and it is not unlikely . . . that in general any given gene has some effect on nearly all parts of the organism." [73] Thus when selection acted directly upon some parts of an organism, it acted indirectly on others. Direct selection pressures upon a character determined by gene *A* could cause selection pressure on selectively neutral characters determined by genes which interacted with gene *A*. Wright believed these indirect selection pressures were generally greater than the order of mutation pressure.

It will be seen that the hypothesis that a selection pressure [of the order of mutation rates] can be the *general* factor making for dominance of wild type, depends upon the assumption that modifiers of dominance (assumed to be sufficiently abundant) are in general so nearly indifferent to selection on their own account that a force of the order of mutation pressure is the *major* factor controlling their fate. With the prevalence of multiple effects in mind it seems doubtful to the present writer whether there are many such genes.[74]

Having rejected Fisher's explanation of the evolution of dominance, Wright proposed an alternative explanation in accordance with his experience with genic interaction systems affecting coat color in guinea pigs:

Probably most geneticists would hold that dominance in general has some immediate physiological explanation. Bateson long ago suggested that pairs of allelomorphs represent the presence or absence of something and that it was to be expected that one dose of an entity would give a result more like that of two doses than like complete absence. There are many reasons which have led to the general abandonment of the presence and absence hypothesis in its literal form. There is still much to be said, however, for the idea that the commonest type of change in a gene is one which partially or completely inactivates it in one or more respects. . . . It seems that in the hypothesis that mutations are most frequently in the direction of inactivation and that for physiological reasons inactivation should generally behave as recessive, at least among factors with major effects, may be found the explana-

73. Sewall Wright, "Fisher's Theory of Dominance," *American Naturalist* 63 (1929): 276–77.

74. Ibid., p. 277.

tion of the prevalence of recessiveness among observed mutations.[75]

Wright was here speaking of a single genetic background. In general he believed that "dominance is a phenomenon of the physiology of development to be associated with the various types of epistatic relationships among factors."[76] In one genetic background allele A_1 might be dominant to allele A_2, but in another genetic background A_2 might be dominant to A_1. Wright's view of dominance was really an extension of his general view of the importance of interaction effects, the same view which so deeply influenced his concept of evolution. Since Fisher was convinced that interaction effects were not important in evolution, he and Wright were never able to agree on the evolution of dominance despite continued communication in the journals.

By the time Fisher published his *Genetical Theory of Natural Selection* in 1930, Wright had put his paper on evolution in nature in nearly final form. Fisher and Wright had corresponded from 1928 on and each had pointed out mistakes in the work of the other. Thus when Wright wrote a review of the *Genetical Theory of Natural Selection* soon after its appearance, he was fully prepared to compare his own theory of evolution with that of Fisher.[77]

Instead of approaching the problem of the distribution of gene frequencies by statistical methods suitable for the analysis of variance in very large populations as Fisher had, Wright approached the problem through analysis of inbreeding by an application of his method of path coefficients. But as a result of the correspondence of 1928–30 Wright could say that "our mathematical results on the distribution of gene frequencies are now in complete agreement as far as comparable, although based upon very different methods of attack."[78] Despite this agreement Fisher and Wright differed markedly in their interpretations of the mathematical results.

75. Ibid., pp. 277–78.
76. Ibid., p. 274.
77. Sewall Wright, "The Genetical Theory of Natural Selection. A Review," *Journal of Heredity* 21 (1930): 349–56.
78. Ibid., p. 35.

Fisher believed that the mass selection of small single gene effects in large populations was the primary process of evolution. In this process the effects of small random fluctuations in the frequencies of genes tended to cancel each other and were therefore negligible. Wright thought the random genetic drift caused by inbreeding was actually very important in evolution. He stated that Fisher "overlooks the role of inbreeding as a factor leading to non-adaptative differentiation of local strains, through selection of which, adaptive evolution of the species as a whole may be brought about more effectively than through mass selection of individuals."[79]

Wright also disagreed with the great emphasis Fisher placed on his "fundamental theorem of natural selection" and believed it needed revision. The theorem, Wright said,

> assumes that each gene is assigned a constant value, measuring its contribution to the character of the individual (here fitness) in such a way that the sums of the contributions of all genes will equal as closely as possible the actual measures of the character in the individuals of the population. Obviously there could be exact agreement in all cases only if dominance and epistatic relationships were completely lacking. Actually dominance is very common and with respect to such a character as fitness, it may safely be assumed that there are always important epistatic effects. Genes favorable in one combination, are, for example, extremely likely to be unfavorable in another.[80]

Having stated his disagreement with Fisher's interpretation of evolution, Wright outlined his own. It is important to quote Wright at some length because of the many erroneous interpretations of his view of evolution which have appeared in print, even recently. Some geneticists have associated with Wright the belief that random drift is the major factor in evolution and that selection is somehow of lesser importance. It is clear in what follows that Wright considered random drift important because it helps create the gene combinations upon which selection acts. The paragraphs quoted from Wright's papers also prove erroneous Ernst Mayr's

79. Ibid., p. 350.
80. Ibid., p. 353.

well-known accusation (made at the Cold Spring Harbor Symposium of 1959) that Wright, along with Fisher and Haldane, was a "beanbag" geneticist. The truth is that from the beginning of his career in genetics Wright was interested in interaction systems of genes, and his concept of evolution in nature rested upon the belief that selection was most effective when acting upon interaction systems of genes rather than upon single genes. Here then is Wright's vision of evolution in nature as he saw it in 1930:

> If the population is not too large, the effects of random sampling of gametes in each generation brings about a random drifting of the gene frequencies about their mean positions of equilibrium. In such a population we can not speak of single equilibrium values but of probability arrays for each gene, even under constant external conditions. If the population is too small, this random drifting about leads inevitably to fixation of one or the other allelomorph, loss of variance, and degeneration. At a certain intermediate size of population, however (relative to prevailing mutation and selection rates), there will be a continuous kaleidoscopic shifting of the prevailing gene combinations, not adaptive itself, but providing an opportunity for the occasional appearance of new adaptive combinations of types which would never be reached by a direct selection process. There would follow thoroughgoing changes in the system of selection coefficients, changes in the probability arrays themselves of the various genes and in the long run an essentially irreversible adaptive advance of the species. It has seemed to me that the conditions for evolution would be more favorable here than in the indefinitely large population of Dr. Fisher's scheme. It would, however, be very slow, even in terms of geologic time, since it can be shown to be limited by mutation rate. A much more favorable condition would be that of a large population, broken up into imperfectly isolated local strains. . . . The rate of evolutionary change depends primarily on the balance between the effective size of population in the local strain and the amount of interchange of individuals with the species as a whole and is therefore not limited by mutation rates. The consequence would seem to be a rapid differentiation of local strains, in itself non-adaptive, but permitting selective increase or decrease of the numbers in different strains and thus leading to relatively rapid adaptive advance of the species as a whole.[81]

This concept of the evolutionary process Wright later termed the "three-phase shifting balance" theory, involving random drift, intrademe, and interdeme selection.

When Wright's long paper, entitled "Evolution in Mendelian Populations,"[82] appeared in 1931, it not only provided corroboration of Fisher's earlier published mathematical considerations by a different method but also provided a significantly different interpretation of the evolutionary process as a whole. In one basic way Wright's efforts resembled those of Fisher. Wright stated in the introduction to his paper that

> the rediscovery of Mendelian heredity in 1900 came as a direct consequence of de Vries' investigation. Major Mendelian differences were naturally the first to attract attention. It is not therefore surprising that the phenomena of Mendelian heredity were looked upon as confirming de Vries' theory. . . . Johannsen's study of pure lines was interpreted as meaning that Darwin's selection of small random variations was not a true evolutionary factor.[83]

Wright considered his own work to be a culmination of the reaction to this point of view.

J. B. S. Haldane

John Burdon Sanderson Haldane was born on 5 November 1892. His father was the physiologist John Scott Haldane. The Haldane family provided an extraordinarily stimulating environment for young J. B. S.[84] His intellectual curiosity was encouraged by his parents in many ways. For example, in 1901 his father took eight-year-old J. B. S. to a lecture by A. D. Darbishire on the recently discovered work of Mendel. Young Haldane was impressed.

81. Ibid., pp. 354–55.
82. *Genetics* 16 (1931): 97–159.
83. Ibid., p. 99.
84. For an account of Haldane's childhood, see Ronald W. Clark, *JBS: The Life and Work of J. B. S. Haldane* (New York: Coward-McCann, 1969), part 1.

Haldane attended Eaton, then entered New College, Oxford, in 1911 on a mathematics scholarship. He excelled in mathematics, gaining first-class honors within a year. Then he switched from mathematics to "Greats," primarily classics and philosophy. In 1914 he won a First in "Greats." He never took a scientific degree. While at New College he attended E. S. Goodrich's biology lectures and found them stimulating. This was his only formal training in biology.

Haldane's practical interest in genetics was aroused even before he went to New College. His sister Naomi began raising guinea pigs for fun in 1908. He and Naomi conducted experiments with them, looking among other things for evidence of Mendelian inheritance. Haldane began reading the available literature on Mendelism, including Darbishire's papers on heredity in mice. From a study of Darbishire's data Haldane believed he had found evidence of linkage. In 1912 he presented this view before a seminar organized by Goodrich. He considered publishing the paper and wrote for advice to Punnett, who advised him to obtain his own data. Together with Naomi and a fellow student, A. D. Sprunt, Haldane began breeding experiments with mice and rats. Sprunt was killed in France early in World War I and Haldane, who was a lieutenant in the Black Watch, decided to publish a preliminary report on the research work in case he also was killed. The report, published in the *Journal of Genetics* in 1915, strongly indicated the existence of linkage in mice.[85] This was one of the first published cases of linkage in mammals.

Haldane was impressed by the work of Morgan and his colleagues on *Drosophila,* and although unable to conduct his researches during the war, he did keep up with the *Drosophila* work by reading journals while stationed in New Delhi during 1917 and 1918. He was especially interested in the problems of linkage and chromosome mapping. The *Drosophila* workers had made chromosome maps by recording frequencies of crossing over between genes on a chromosome and making the chromosome distance between any two genes proportional to the frequency of crossing over between them. But it was well known that the measured distance between two distant loci on a chromosome map was less than the sum of the distances between loci located between the original two. Haldane began research on the linkage problem immediately after the war and published two papers on the subject in 1919. In the first he derived formulas for the probable errors of calculated linkage values.[86] He hoped geneticists would check their linkage data with the probable errors to see if the theory of crossing over (and chromosome mapping) was actually supported by the data. In the second paper he developed a theory to correct the discrepancies of chromosome maps based only upon linkage values. His theory permitted "the calculation of one of the cross-over values for three factors from the other two, with a probable error of less than 2%" and could also be used "to calculate the total length of a chromosome, and the number of double and triple cross-overs to be expected in a large distance."[87] Haldane found his theory fit plant data accurately but the *Drosophila* data less well. The method used by Haldane in these papers was typical of his life-long approach to genetical problems. He discovered problems in the data of others for which he offered theoretical solutions, then checked his ideas with the data of others.

In 1922 Haldane spoke with the mathematician H. T. J. Norton of Trinity College, Cambridge. Norton had prepared the selection table in Punnett's *Mimicry in Butterflies* (1915). Haldane discovered that with the exception of Warren's short paper in 1917, Norton's table was still the only available analysis of the mathematical consequences of selection. He decided to undertake this investigation. By the time his book *The Causes of Evolution* appeared in 1932, he had published nine

85. J. B. S. Haldane, A. D. Sprunt, and N. M. Haldane, "Reduplication in Mice," *Journal of Genetics* 5 (1915): 133–35.

86. J. B. S. Haldane, "The Probable Errors of Calculated Linkage Values, and the Most Accurate Method of Determining Gametic from Certain Zygotic Series," *Journal of Genetics* 8 (1919): 291–97.

87. J. B. S. Haldane, "The Combination of Linkage Values, and the Calculation of Distance between the Loci of Linked Factors," *Journal of Genetics* 8 (1919): 308, 309.

papers under the collective title "A Mathematical Theory of Natural and Artificial Selection."

Haldane published the first paper in the series in 1924. He opened with the statement:

> A satisfactory theory of natural selection must be quantitative. In order to establish the view that natural selection is capable of accounting for the known facts of evolution we must show not only that it can cause a species to change, but that it can cause it to change at a rate which will account for present and past transmutations.[88]

The purpose of his series of papers was to quantify the theory of natural selection. In the first paper Haldane derived mathematical expressions and computed tables for the effect of selection on simple Mendelian populations. He assumed random mating, an infinite population, separate generations, complete dominance, perfect Mendelian segregation, and no change of selection intensities from generation to generation. The cases he treated varied from selection in self-fertilizing populations, to selection of dominant or recessive autosomal and sex-linked characters, to prenatal selection. The method he used was to derive recurrence equations from which the proportion of gametes in one generation could be computed from the proportion in the preceding generation. Most of these recurrence equations were nonlinear and Haldane had to work out approximate solutions.

He applied the model to the case of the peppered moth *Amphidasys betularia*. A dominant melanic form had first appeared in this variety at Manchester in 1848 and before 1901 it had replaced the recessive form. Haldane found that "the fertility of the dominants must be 50% greater than that of the recessives," which he called a "not very intense degree of natural selection."[89] But it was far more intense than the selection pressures which Fisher believed were important in the evolution of species. Haldane, like Morgan, placed much

88. J. B. S. Haldane, "A Mathematical Theory of Natural and Artificial Selection. Part 1," *Transactions of the Cambridge Philosophical Society* 22 (1924): 19.
89. Ibid., p. 26.

more emphasis upon the selective importance of a single gene effect than did Fisher.

In succeeding parts of the series Haldane modified his initial assumptions, then explored the mathematical consequences of selection. In part 2 (1924)[90] he treated selection with partial self-fertilization, inbreeding, assortative mating, and selective fertilization. Part 3 (1926)[91] covered the problems of selection with incomplete dominance. Part 4 (1927)[92] was devoted to a study of the consequences of selection when generations were overlapping instead of separate. The finite difference equation Haldane had previously developed was inapplicable, and he here developed another finite difference equation for the change in the proportions of genotypes between times t_1 and t_2. In part 5 (1927)[93] he treated the problem of the survival of new mutations, dominant or recessive, and examined the balance between mutation pressure and selection pressure. He found, as had Fisher, that the survival of very rare recessive mutations was a stochastic process which depended little on the deterministic effects of selection.

There was a three-year gap, from 1927 to 1930, between the appearance of part 5 and part 6. During this time Haldane wrote several articles on the process of evolution in general and joined in the dispute between Fisher and Wright regarding the evolution of dominance. By 1927 Haldane's general approach to evolution was settled. As a young man he was interested in single gene effects, probably because of the influence of the English Mendelians and the *Drosophila* workers. He believed that selection was the most powerful force in evolutionary change and found Morgan's general view of evolution by single gene replacement appealing. Up to 1927 Haldane treated populations as very large or infinite and selection as completely deterministic, except for the fixation of

90. J. B. S. Haldane, "A Mathematical Theory of Natural and Artificial Selection. Part 2," *Proceedings of the Cambridge Philosophical Society. Biological Sciences* 1 (1924): 158–63.
91. J. B. S. Haldane, "A Mathematical Theory of Natural and Artificial Selection. Part 3," *Proceedings of the Cambridge Philosophical Society* 23 (1926): 363–72.
92. Ibid., pp. 607–15.
93. Ibid., pp. 838–44.

rare recessives which depended upon a stochastic process. Unlike Fisher, he emphasized the importance of high selection pressures caused by single mutations. But he agreed with Fisher about the deterministic effect of mass selection and the importance of this process in evolution. Wright believed that the most effective population size was much smaller than did either Haldane or Fisher and that the effect of selection on single genes was less important than the effect of selection upon interaction systems of genes.

Haldane thought his investigations exemplified the possibilities of Darwinian selection. Like Fisher and Wright, he found it necessary to defend the principle of natural selection even as late as 1929:

> Quantitative work shows clearly that natural selection is a reality, and that, among other things, it selects Mendelian genes, which are known to be distributed at random through wild populations, and to follow the laws of chance in their distribution to offspring. In other words, they are an agency producing variation of the kind which Darwin postulated as the raw material upon which selection acts.[94]

Later in 1929 Haldane wrote that he believed in the importance of chromosomal alterations and polyploidy as factors in evolution.[95] In this he tended to agree with Wright rather than Fisher and the Darwinian tradition.

Early in 1930 Haldane entered the controversy over the evolution of dominance. First he argued in agreement with Wright that not enough modifiers of the sort postulated by Fisher were available in natural populations. Then he proposed an alternative hypothesis:

> Adopting Goldschmidt's view that genes are catalysts acting at a definite rate, there is no obvious way of distinguishing those which act at more than a certain rate. E.g., if an enzyme can oxidize a certain substance as quickly as it is formed, no visible result arises from doubling the amount of that enzyme. Hence, while a minus mutation (diminution of activity) of a normal gene may yield a recessive type, a plus

94. J. B. S. Haldane, "Natural Selection," *Nature* 124 (1929): 444.
95. J. B. S. Haldane, "The Species Problem in the Light of Genetics," ibid., pp. 514–16.

> mutation is often unobservable. Now on this hypothesis we have to explain why a wild-type gene generally has a factor of safety of at least 2, as is shown by the fact that one wild-type gene has nearly the same effect as two. If we imagine a race whose genes were only just doing the work required of them, then any inactivation of one of a pair of genes would lead to a loss of total activity. Thus if A_1A_1 can just oxidize all of a certain substrate as fast as it is formed, its inactivation will produce a zygote A_1a which can only oxidize about half. If now A_1 mutates A_2, which can oxidize at twice or thrice the rate of A_1, if necessary, no effect will be produced, i.e., A_1A_2 and A_2A_2 zygotes will be indistinguishable from A_1A_1. But A_2a will be normal. Hence A_2a zygotes will have a better chance of survival than A_1a, and A_2 will be selected.
>
> In other words the modifiers postulated by Fisher are probably the normal allelomorphs of mutant genes, and the Fisher effect is rather to accentuate the activity of genes already present than to call up new modifiers.[96]

Haldane thus solved the problem of the evolution of dominance by means of the selection of sizable mutations, in accordance with his general view of evolution by single gene replacement.

Between 1930 and 1932 Haldane published four more parts to his "Mathematical Theory of Natural and Artificial Selection." Part 6 (1930) [97] dealt with the effects of isolation and migration. In part 7 (1931) [98] he finally explored a case where selection intensity was not constant from generation to generation, specifically when selection intensity was a function of mortality rate. In part 8 (1931) [99] he started with the supposition that a population with interacting genes was very close to genetic equilibrium (which Haldane termed "metastable equilibrium"). He then considered the case where two genes might be deleterious singly but advantageous together and outlined the most favorable conditions for the replacement of one interaction system by another. He concluded that "in

96. J. B. S. Haldane, "A Note on Fisher's Theory of the Origin of Dominance, and on a Correlation between Dominance and Linkage," *American Naturalist* 64 (1930): 88.
97. *Proceedings of the Cambridge Philosophical Society* 26 (1930): 220–30.
98. Ibid. 27 (1931): 131–36.
99. Ibid., pp. 137–42.

many cases related species represented stable types . . . and the process of species formation may be a rupture of the metastable equilibrium. Clearly such a rupture will be specially likely where small communities are isolated."[100] Haldane submitted this paper on 20 November 1930 before he could have read Wright's "Evolution in Mendelian Populations." Thus he independently derived results in agreement with those Wright had derived earlier but had not yet published in substantial form. But Haldane believed that small partially isolated communities were far less common in natural populations than did Wright. In part 9 (1932),[101] the last to appear before the publication of *The Causes of Evolution,* Haldane treated the effects of rapid selection, a process which Fisher considered relatively unimportant in the evolution of natural populations.

In January 1931 Haldane delivered a series of lectures entitled "A Re-examination of Darwinism." The series was published as a book in 1932 with the title *The Causes of Evolution.*[102] The book contained an exposition of his general view of evolution. He intended, as had Fisher in the *Genetical Theory of Natural Selection* and Wright in "Evolution in Mendelian Populations," to dispel the belief that Mendelism had killed Darwinism. He headed the first chapter with the quote "Darwinism is dead." He raised most of the charges brought against Darwinian selection between 1900 and 1930 and, while emphasizing his own view that "natural selection is an important cause of evolution," concluded that "the criticism of Darwinism has been so thorough-going that a few biologists and many laymen regard it as more or less exploded."[103]

Included in *The Causes of Evolution* was a technical appendix summarizing the most important points developed in the first nine parts of "A Mathematical Theory of Natural and Artificial Selection." Haldane also analyzed the contributions of Fisher and Wright in the appendix. He agreed with much of Fisher's work and relied heavily upon *The Genetical Theory of Natural Selection* in writing the appendix. The basic issues on which Haldane differed from Fisher concerned the evolution of dominance and the intensity of selection pressure caused by a single gene effect in a natural population. Less basic differences were Haldane's greater emphasis upon migration, genic interaction, and discontinuities in evolution. Haldane agreed with Wright's view that evolution should be slow in very small populations but disagreed that evolution was also slow in very large populations. He thought Wright overemphasized the importance of random genetic drift. But he agreed with one of Wright's basic positions:

> Wright's theory certainly supports the view taken in this book that the evolution in large random-mating populations, which is recorded by paleontology, is not representative of evolution in general, and perhaps gives a false impression of the events occurring in less numerous species. It is a striking fact that none of the extinct species, which, from the abundance of their fossil remains, are well known to us, appear to have been in our own ancestral line. Our ancestors were mostly rather rare creatures.[104]

After discussing the views of Fisher and Wright as well as his own, Haldane closed the *Causes of Evolution* with the 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.[105]

In the light of modern population genetics, this statement was indeed prophetic.

Having examined the views of evolution of Fisher, Haldane, and Wright, it is illuminating to compare the general view each took of the work of the other two in the early

100. Ibid., p. 141.
101. Ibid., 28 (1932): 244–48.
102. (London: Longmans, Green, 1932).
103. Ibid., pp. 20, 32.
104. Ibid., pp. 213–14.
105. Ibid., p. 215.

1930s. Haldane stated that the work of Wright "resembles the work of Fisher more than that of Haldane."[106] Wright believed that the strong emphasis upon the deterministic effects of mass selection of single genes in the work of Fisher and Haldane distinguished their work sharply from his own, which emphasized the selection of interaction systems of genes. Fisher thought Wright and Haldane failed to appreciate the importance of very small selection pressures acting over long periods of time in the evolution of natural populations. He often lumped Wright and Haldane together as critics of his views. Thus the relationship between the three appears to have been symmetrical.

The work of Fisher, Haldane, and Wright up to 1932 is the culmination of this account. It began with the disagreement which arose immediately upon the publication of Darwin's *Origin of Species* between the adherents of continuous evolution and the adherents of discontinuous evolution. Even Darwin's friends Huxley and Galton opposed his view of the continuity of evolution. The idea of discontinuous evolution was reinforced by the work of William Bateson in the 1890s. His work stimulated heated opposition from the biometricians, who believed in Darwin's idea of selection by minute differences as the mechanism of evolution. When Mendelian heredity was rediscovered in 1900 Bateson grabbed it as a support for discontinuous evolution and the biometricians reacted by attacking Mendelism, with the result that in the first decade of this century Mendelism and Darwinism were generally thought to be contradictory. The consequences inferred from the pure line theory helped to further the split between Mendelian heredity and Darwinian selection. Many Mendelians thought the pure line theory necessarily led to de Vries's mutation theory rather than to Darwin's idea of continuous evolution. But between 1908 and 1918 crucial selection experiments demonstrated that selection of small differences could change a population significantly and permanently. By 1918 many prominent geneticists were promulgating the view that

106. Ibid., p. 212.

Mendelian heredity and Darwinian selection were complementary rather than contradictory. Fisher, Haldane, and Wright then quantitatively synthesized Mendelian heredity and natural selection into the science of population genetics. The work of all three was to some extent a reaction against Mendelians who claimed that natural selection was of subordinate importance in evolution.

Conclusions

The story of the origins of population genetics illustrates three important patterns in the history of science, all of which contradict the current popular conception of science. First, it illustrates that personality conflicts are sometimes very important in the development of scientific ideas. The intense antagonisms generated by Bateson's dislike of Pearson and Weldon and vice versa contributed to a delay of more than a decade in the understanding that Mendelism and Darwinism were complementary. If Bateson and Pearson had collaborated instead of fought, population genetics would have gained a significantly earlier start. Second, the story illustrates that the acceptance by scientists of a new idea is sometimes more dependent upon its a priori acceptability than upon its scientific proof. The pure line theory is an example. It was accepted, as well as the selection theory associated with it, by almost all geneticists even though conclusive experimental proof was totally absent. Third, the story of the origins of population genetics illustrates that a field of science can begin with a theoretical structure which is far from consistent. Population genetics was founded by three men, each of whom produced a basic model of evolutionary change. All three agreed upon the importance of natural selection, but each had a significantly different approach. The problem was that each could cite examples from natural populations to support his approach. Population genetics has grown enormously and attracted much attention since its inception, but population geneticists have yet to remove from the theoretical framework many of the basic differences of approach already visible in 1932 in the work of Fisher, Haldane, and Wright. For

example, each proposed a model for the evolution of dominance and these have yet to be authoritatively reconciled. This situation results because small parameters can effect great changes in populations over a surprisingly small number of generations. But the isolation of all significant parameters affecting population change is difficult even under the best conditions with populations in the laboratory. With populations in nature this problem of course greatly increases. Thus with the gap between theoretical models and available observational data so large, population genetics began and continues with a theoretical structure containing obvious internal inconsistencies.

APPENDIX

Galton, Pearson, and the Law of Ancestral Heredity

THE CONFUSION OF BIOLOGISTS CONCERNING THE MEANING AND application of Galton's law of ancestral heredity will perhaps be more understandable if the various interpretations given it by Galton and Pearson are distinguished.[1] Galton contributed to the confusion over his law in three ways.

First, Galton's forms A and B of his law are mathematically inconsistent. Consider the following situation. Suppose a mid-parent has a deviation of D_1 from the mean of the population. Then the offspring will have an average deviation of $D = \frac{2}{3} D_1$ by the law of regression. Galton's form A says the mid-parent contributes one half of the heritage of the offspring, or $\frac{1}{2}(\frac{2}{3} D_1)$, the mid-grandparent contributes $\frac{1}{4}(\frac{2}{3} D_1)$, etc. Then the total contribution of the ancestors to the deviation of the offspring is

$$D = \tfrac{1}{2}(\tfrac{2}{3} D_1) + \tfrac{1}{4}(\tfrac{2}{3} D_1) + \tfrac{1}{8}(\tfrac{2}{3} D_1) + \cdots = \tfrac{2}{3} D_1.$$

In this formulation the series $\frac{1}{2}$, $\frac{1}{4}$, $\frac{1}{8}$ . . . appeals to Galton because it sums to 1 and accounts for the entire heritage of the offspring. But form B of Galton's law states that the mid-parent contributes one half of its *own* deviation, or $\frac{1}{2} D_1$, and that the mid-grandparent contributes $\frac{1}{4} D_2$, etc., where D_1, D_2, D_3, etc., are the deviations of the individual ancestral generations. Form B of Galton's law thus generates the following series:

$$D = \tfrac{1}{2} D_1 + \tfrac{1}{4} D_2 + \tfrac{1}{8} D_3 + \cdots = \tfrac{2}{3} D_1.$$

The problem is that the "contribution" of any given ancestral generation is different acccording to whether one uses Galton's form A or form B. In form A the contribution of the mid-parent to the deviation of the offspring is $\frac{1}{2}(\frac{2}{3} D_1)$, or $\frac{1}{3} D_1$; in form B the contribution of the mid-parent to the