# THE FUNDAMENTAL THEOREM OF NATURAL SELECTION

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## CONTENTS

*The fundamental theorem of natural selection was a valiant attempt by R. A. Fisher to fit a quart into a pint pot.*

The present author reviewing *Population Genetics* by Ewens, 1969*a* (Edwards, 1969).

*Many authors have maintained that the theorem holds only under very special conditions, while only a few (e.g. Edwards, 1967) have thought that Fisher may have been correct – if only we could understand what he meant! It will be shown here that this latter view is correct.*

Price, 1972.

*My own reason for not including a planned chapter on the fundamental theorem is...[that] in spite of many efforts I am still not satisfied that I am able to provide an account that does the theorem justice.*

The present author in the Epilogue to *Foundations of Mathematical Genetics* (Edwards, 1977).

## I. INTRODUCTION

R. A. Fisher enunciated his Fundamental Theorem of Natural Selection in Chapter II of The Genetical Theory of Natural Selection (1930):

The rate of increase in fitness of any organism at any time is equal to its genetic variance in fitness at that time.

For 42 years after its publication the theorem was universally misunderstood and its name often attached either to a simpler approximate theorem (which was true) or to a general theorem about the mean fitness never decreasing (which was not). Then in 1972 the late G. R. Price (who was also jointly responsible for the notion of an Evolutionarily

R. A. FISHER in 1929
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Stable Strategy; Maynard Smith and Price, 1973) published a detailed analysis and explanation (Price, 1972) which led in due course to Ewens's clearer formulation of the theorem and hence to its wider acceptance (Ewens, 1989; for some background discussion, see Edwards, 1990).

The purpose of the present review is not only to give an account of the Fundamental Theorem as now understood, but to lay to rest the misunderstandings and misnamings of earlier years. In order to achieve this it will be necessary to review some statements which are now best forgotten, since this paradoxical activity is the only way to clear away the confusion which has surrounded the theorem. The authors of the recalled statements can rest assured that not only have they kept distinguished company, but also that to change one's view of the Fundamental Theorem has notable precedents. However, I shall not review the arguments of Price and Ewens in favour of the present interpretation of the theorem, except in so far as they are implicit in what follows. I believe them to be correct, and the reader who still harbours lingering doubts should study Price (1972) and Ewens (1989) for himself.

It will be helpful at the outset if we keep in mind the following simple 'growth-rate' theorem:

In a subdivided population the rate of change in the overall growth-rate is proportional to the variance in growth rates.

This elementary theorem is applicable wherever there are differential growth-rates, in economics for example (Edwards 1987 a) as well as in biology. It opens a window on to the Fundamental Theorem, yet seems never to have been published in its own right, by Fisher or anyone else. Fisher clearly possessed it in 1930, but it was not until many years later that it came to be given explicitly by writers commenting on the Fundamental Theorem. I first saw it in the text-book by C. C. Li (1955) as a 'simplified version of Fisher's *fundamental theorem of natural selection*'. Simplified it certainly was, for it omitted mating; in a subsequent edition (1976) Li replaced this version by another which, as we shall see, has been one of the two common misinterpretations of the Fundamental Theorem. Somewhat paradoxically, another source for this elementary theorem is the section entitled 'An extension of Fisher's Fundamental Theorem of Natural Selection to include interpopulation selection' in Crow (1955), for if the genic variances are zero all that remains is the interpopulation variance.

The growth-rate theorem is easily proved: Let a population be subdivided into $k$ parts in proportions $p_i$ ($i = 1, 2, \ldots, k$) and let the $i$th part change in size by a factor $w_i$ in unit time (its 'growth-rate'). At the end of the unit time interval the new proportion of the $i$th part will be $p_i' = p_i w_i / w$, where $w = \Sigma p_i w_i$ is the overall growth rate. The new overall growth rate $w' = \Sigma p_i' w_i$ is therefore equal to $\Sigma p_i w_i^2 / w$ and the change in the overall growth-rate, $w' - w$, is $(\Sigma p_i w_i^2 - w^2) / w$. But the numerator of this expression is simply the variance of the $w_i$ by definition (say $v$), being their expected squared value minus their squared expected value. Thus $w' - w = v/w$ and the theorem is proved. The constant of proportionality, $1/w$, is of course just a scaling factor: dividing both sides by $w$ leads to $w'/w - 1 = v/w^2$, showing that the proportionate change is equal to the square of the coefficient of variation. A continuous version of the theorem is easily obtained by proceeding to a limit, the growth in each sub-population then being exponential.

The growth-rate theorem exactly captures the vague notion that the more variable are the growth-rates the more quickly will the most rapidly-growing parts of the population (or sectors of the economy) come to dominate the rest. Eventually dominance by the fastest will be complete, all variability in growth-rates will have vanished, and no further increase in the overall growth-rate can occur. It is as though the process of change, or evolution, consumes the variability. It was the intrinsic difficulty of adapting this simple theorem to the complexities of Mendelian genetics, coupled with Fisher's cryptic exposition in *The Genetical Theory*, which caused his successful attempt to be misunderstood for so long.

## II. BACKGROUND

It is to Adam Smith's *An Inquiry into the Nature and Causes of the Wealth of Nations* (1776) that we must turn for the germ of the idea behind the Fundamental Theorem. In Book IV: *Of Systems of Political Economy* he wrote:

As every individual, therefore, endeavours as much as he can both to employ his capital in the support of domestic industry, and so to direct that industry that its produce may be of the greatest value; every individual necessarily labours to render the annual revenue of the society as great as he can. He generally, indeed, neither intends to promote the public interest, nor knows how much he is promoting it. By preferring the support of domestic to that of foreign industry, he intends only his own security; and by directing that industry in such a manner as its produce may be of the greatest value, he intends only his own gain, and he is in this, as in many other cases, led by an invisible hand to promote an end which was no part of his intention. Nor is it always the worse for the society that it was no part of it. By pursuing his own interest he frequently promotes that of the society more effectually than when he really intends to promote it.

From this idea it is but a small step to the realization that an economy progresses not merely because the efforts of individual producers to better themselves raise the average level of production, but also because the 'invisible hand' will drive inefficient producers out of business and thus raise the average still further. As Sober (1984) remarked, 'The Scottish economists offered a non-biological model in which a selection process improves a population as an unintended consequence of individual optimization', and he saw this as one of the influences in the formation of Darwin's views on the effects of natural selection. We can only speculate on whether Fisher was familiar with these ideas in economics in the 1920s; if so, a possible source would have been the economist J. Maynard Keynes, whose *A Treatise on Probability* was published in 1921 and whom Fisher had known since his undergraduate days (Box, 1978). He will, however, certainly have read Darwin's comment: 'The larger and more dominant groups thus tend to go on increasing in size; and they consequently supplant many smaller and feebler groups' (*The Origin of Species*, p. 428; Darwin, 1859).

At the time when Fisher entered on his researches the importance of heritable variation as the raw material on which natural selection acts was not well understood, and the prevailing intellectual atmosphere was one of doubt as to whether Darwinian natural selection could account fully for evolutionary change. Furthermore, no one had yet successfully quantified this variation mathematically. Indeed, not until Francis Galton had statisticians learnt to regard biological variability as intrinsically interesting, in contrast to variability in physics and astronomy which they had been accustomed to think of as 'error'. Karl Pearson, in his many papers on evolution, had pursued the

mathematical study of biological variation, but it was the young Fisher who saw the overwhelming advantages of working not with the standard deviation but its square, which he christened the variance in his paper *The correlation between relatives on the supposition of Mendelian inheritance* (Fisher, 1918 a). As he explained in a contemporary article in the *Eugenics Review*: 'This mean square deviation I term the variance, and use it as a measure of variability, by reason of this important property, namely, that two independent causes of variability acting together produce a variance which is the sum of the variances produced by either separately' (Fisher, 1918 b). Indeed, he went so far as to say, in the opening sentence of this article, 'The great service which the modern development of statistics has rendered to eugenics is that it supplies a definite method of measuring and analysing variability'.

Throughout the 1920s, during the gestation of *The Genetical Theory of Natural Selection*, Fisher was fond of quoting Darwin's dictum, from Chapter II of *The Origin of Species*, that 'wide ranging, much diffused, and common species vary most'. 'The present note', he wrote in his major 1922 paper (Fisher, 1922 a), 'is designed to discuss the distribution of the frequency ratio of the allelomorphs of dimorphic factors, and the conditions under which the variance of the population may be maintained'. It was a remarkable 'note', for it introduced to the world not only the concept of stable polymorphism through heterozygotic advantage but also the chain-binomial model for gene-frequency change and the associated concept of the distribution of gene frequencies. To handle the chain-binomial model Fisher introduced the diffusion approximation, thus inaugurating stochastic diffusion theory (see Kendall, 1990). In addition, he applied the Galton–Watson branching process to the survival of an individual gene and handled it by functional iteration. (For further comments on this paper and its impact, see Edwards, 1978, 1990; the branching-process model is also described in Fisher's simultaneous publication 1922 b which carries the date 'Feb. 2nd, 1921'.)

Fisher's 1922 investigations were thus motivated by a desire to investigate the importance of the various factors affecting the variance of a population. Stochastic losses due to finite population size will cause a slow decay, but the major contributions will be the gain due to mutation and the loss due to selection: 'The decay in the variance of a species breeding at random without selection, and without mutation, is almost inconceivably slow: a moderate supply of fresh mutations will be sufficient to maintain the variability. When selection is at work even to the most trifling extent, the new mutations must be much more numerous to maintain equilibrium… 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 [quoted above]'.

Armed with his appropriate measure of variability and inspired by Darwin's work, it was thus natural that Fisher should proceed to quantify the relationship between the variability in the genetic contributions of individuals to subsequent generations, and the rate at which the population changes in consequence. In 1926, in a note in *Nature* with E. B. Ford, he wrote 'it is easily demonstrable that in species in which a higher proportion of the total variance is ascribable to genetic causes, the effective selection will be more intense than in species in which the variance is to a larger extent ascribable to environmental variations' (Fisher & Ford, 1926; repeated in Fisher & Ford 1928). As

many have remarked, when Fisher wrote 'it is easily demonstrable' you knew you were in for a long haul.

On 13 November 1928 Fisher wrote to Leonard Darwin, Charles Darwin's fourth son and Fisher's early mentor, telling him how *The Genetical Theory of Natural Selection* was progressing: 'I have finished drafts of Chapters II [*The Fundamental Theorem of Natural Selection*] and III, but not yet started IV. They are at your disposal but I do not want to press a lot of heavy reading on you. Chapter II is heavy. ... [P.S.] Thank you ever so much for real encouragement' (Bennett, 1983). On the only occasion on which I met Lady Fisher (24 June 1974) I asked her about *The Genetical Theory*. She said that except for Chapters IV and V Fisher dictated it to her as he paced up and down their living room, she taking it down longhand. She added that the Fundamental Theorem 'came to him as he dictated'. Fisher's daughter and biographer, Mrs Joan Fisher Box, had earlier told me that he had been dissatisfied with its exposition, but could not see how to improve it (Edwards, 1990; Box, 1978, adds that the period of dictation was between October 1928 and June 1929).

Calling the relative genetic contributions of individuals their fitnesses, Fisher sought a relationship between the variance in fitness in the population and the fitness of the whole population (as measured by the mean of the individual fitnesses). It was presumably at this stage that he discovered the exact growth-rate theorem given in the Introduction above. He will instantly have seen that as it stood it was incapable of direct application to the evolutionary problem for the simple but highly complicating reason that the Mendelian mechanism ensures that although a population may be said to have a continuing existence, the individuals which constitute it do not. The variability which passes from one generation to the next through the medium of reproduction is related to, but not identical to, the phenotypic variability manifest in the reproducing generation.

Appreciation of this point will have come naturally to Fisher. In *The correlation between relatives* he had already shown how the total genotypic variance at a single locus in a population, that is, the variance contributed by the variability of genotypes in an environment assumed uniform, could be considered as the sum of two components. The first component, called the genetic variance, is due to the additive effects of the genes ('an additive part which reflects the genetic nature without distortion'), whilst the second, residual component, the dominance variance, is due to the non-additive effects of the genes. The basic idea comes from linear regression: regress the genotypic values on the number (o, 1 or 2) of genes of a particular allelic type and the resultant analysis of variance separates the linear ('genetic') and the residual ('dominance') effects. (For more information consult, for example, the books by Falconer, 1989, or Edwards, 1977).

Here I digress for a moment to introduce a uniform terminology, for there has been a change of usage since Fisher first wrote. He used the word 'genetic' straightforwardly as the adjective from the word 'gene', so that by 'genetic variance' he meant the variance contributed by the genes acting additively. It would have been consistent with his 1918 usage to have written, for example, 'The genotypic variance (in a uniform environment) is the sum of the genetic and dominance variances'. Unfortunately, in an attempt at clarification, some writers started to refer to the 'additive genetic variance', which carried the implication that some of the genetic variance was non-additive.

Before long, therefore, 'genetic' replaced 'genotypic' as in 'The total genetic variance is the sum of the additive genetic variance and the dominance variance'. Crow and Kimura (1970), surveying the resultant confusion, recommended using the word 'genic' as the adjective from 'gene', with the statement thus becoming 'The genotypic variance is the sum of the genic variance and the dominance variance'. I shall adhere to this usage; as it happens, the adjective 'genic' was used by Fisher (1932), though it was actually coined by C. B. Bridges ten years earlier.

### III. THE FUNDAMENTAL THEOREM OF NATURAL SELECTION

Price's (1972) masterly analysis of the Fundamental Theorem is wholly convincing, but it is not the simplest approach to the theorem, which was provided by Ewens (1989). Ewens pointed out that 'the Fundamental Theorem as properly understood ... is exact in discrete time and thus not specifically a continuous-time result'. Both Fisher's original derivation and Price's commentary are couched in the language of continuous time and the differential calculus, and part of the lack of understanding of the theorem has been the erroneous view that whilst a continuous-time version might be correct if properly interpreted, no exact discrete-generation version exists (Edwards, 1967, 1977). I now give Ewens's proof of the theorem for a single multiallelic locus. In his view 'the discrete-time calculation ... was clearly well-known to [Fisher] and possibly formed the basis of [the] continuous-time result'. I shall refer to my *Foundations of Mathematical Genetics* ('FMG'; Edwards, 1977) for background information, but using capital $A$ rather than lower-case $a$ for the genes so as to conform to Ewens's notation and release $a$ for another purpose.

The essence of Price's interpretation is the recognition of the fact that the Fundamental Theorem refers to the *partial change* in mean fitness, not the total change. This will be defined and derived in the third part of the proof which follows.

Consider a discrete-generation model and let $P_{ii}$ be the frequency of genotype $A_i A_i$, and $2P_{ij}$ the frequency of genotype $A_i A_j$. (Hardy–Weinberg equilibrium is not assumed.) The frequency of $A_i$ is then $p_i = \Sigma_j P_{ij}$ and if the fitness of $A_i A_j$ is $w_{ij}$ then the mean fitness is $w = \Sigma_{i,j} P_{ij} w_{ij}$. In the adult population the frequency of $A_i$ will therefore be $p_i' = \Sigma_j P_{ij} w_{ij}/w$. We now define the *average excess* $a_i$ of gene $A_i$ in conformity with Fisher (1930, 1958), but in the words of FMG p. 12:

With respect to any character, the average excess of a gene is the difference between the mean for that sub-population consisting of all the homozygotes and half the heterozygotes which carry that gene, and the mean of the whole population.

Hence in respect of the character 'fitness'

$$a_i = (P_{ii} w_{ii} + \sum_{j \neq i} P_{ij} w_{ij})/\Sigma_j P_{ij} - w = \sum_j P_{ij} w_{ij}/p_i - w. \tag{1}$$

Notice that the change in the frequency of $A_i$ through the action of the differential fitnesses, $\Delta p_i = p_i' - p_i$, may now be expressed in terms of the average excess:

$$\Delta p_i = \sum_j P_{ij} w_{ij}/w - p_i = (p_i/w)(\sum_j P_{ij} w_{ij}/p_i - w) = p_i a_i/w. \tag{2}$$

In passing, this proves the obvious fact that the weighted sum of the average excesses is zero, $\Sigma_i p_i a_i = 0$, since necessarily $\Sigma_i \Delta p_i = 0$.

The second of the new concepts which Fisher developed for the Fundamental Theorem is that of the *average effect* $\alpha_i$ of the gene $A_i$ on the deviation of the fitness of a genotype from the mean fitness $w$. Even in the simplest single-locus model, the effect of a gene on the fitness of a genotype depends not only on which allele it is, but on which allele accompanies it in the genotype, except in the special case of no dominance in fitness, when the deviation from the mean fitness is determined by the simple sum of the effects of the two genes: $w_{ij} - w = \alpha_i + \alpha_j$. 'Then the effect on the fitness of an individual whose genotype contains an $A_j$ gene of replacing that gene by an $A_i$ gene is $\alpha_i - \alpha_j$' (Ewens, 1989). In the presence of dominance, however, we may not speak unambiguously of the effect of the gene $A_i$, but we can compute its average effect by appealing to the idea of regression, regressing the fitness of genotypes on the numbers of each allele present to find the 'additive effects' of the alleles (Fisher, 1918; see above, Section II). We may use Fisher's own words from 1941, which was the only occasion on which he was mathematically explicit (his attempts at verbal definition have not always corresponded exactly with this (Falconer, 1985)):

The direct mathematical measure of the average effect of a...gene substitution is the partial regression...of the genotypic measurement on the numbers 0, 1 or 2 of the allelomorphic genes [alleles] in each genotype. This is the natural measure of the average effect of a gene substitution.

We now implement this definition by the standard regression procedure of finding the values of the $\alpha_i$ which minimize the residual sum of squares $\Sigma_{i,j} P_{ij} (w - w_{ij} + \alpha_i + \alpha_j)^2$. The normal equations are, for all $i$, $\Sigma_j P_{ij} (w - w_{ij} + \alpha_i + \alpha_j) = 0$, and on expanding this and recalling that $\Sigma_j P_{ij} w_{ij} = p_i a_i + p_i w$ from the expression (1) for the average excess $a_i$, we have

$$p_i \alpha_i + \sum_j P_{ij} \alpha_j = p_i a_i. \qquad (3)$$

The genic variance is the sum of squares removed by the regression:

$$v = \sum_{i,j} P_{ij} (\alpha_i + \alpha_j)^2 = 2\sum_{i,j} P_{ij} \alpha_i^2 + 2\sum_{i,j} P_{ij} \alpha_i \alpha_j$$

$$= 2\sum_i p_i \alpha_i^2 + 2\sum_{i,j} P_{ij} \alpha_i \alpha_j.$$

Now

$$\sum_j P_{ij} \alpha_i \alpha_j = p_i (a_i - \alpha_i) \alpha_i \quad \text{from (3)}$$

so

$$2\sum_{i,j} P_{ij} \alpha_i \alpha_j = 2\sum_i p_i (a_i - \alpha_i) \alpha_i$$

and we arrive at

$$v = 2\sum_i p_i \alpha_i a_i, \qquad (4)$$

Fisher's expression for the genic variance in terms of the average effects $\alpha_i$ and average excesses $a_i$ of the genes (Fisher, 1930, though the formulation involving multiple alleles is 1958).

The third and final part of the proof of the theorem is to show that the partial change in the mean fitness $w$ due to changes in the genotypic frequencies $P_{ij}$ from one generation to the next ($P'_{ij}$) is precisely equal to $v/w$. For it is a standard result of the regression model that the weighted mean departure of the genotypic fitnesses from their regression values is zero, or $0 = \Sigma_{i,j} P_{ij}(\alpha_i + \alpha_j)$, and adding the mean fitness $w$ to both sides leads to $w = \Sigma_{i,j} P_{ij}(w + \alpha_i + \alpha_j)$ since $\Sigma_{i,j} P_{ij} = 1$. Thus the change in $w$ due only to the change in the genotype frequencies $P_{ij}$ and not including changes in $w$ and the $\alpha_i$ is

$$\delta w = \sum_{i,j} (P'_{ij} - P_{ij})(w + \alpha_i + \alpha_j)$$

$$= \sum_{i,j} (P'_{ij} - P_{ij})(\alpha_i + \alpha_j)$$

$$= 2\sum_{i} \left(\alpha_i \sum_{j}(P'_{ij} - P_{ij})\right)$$

$$= 2\sum_{i} \alpha_i \Delta p_i \quad \text{since} \quad p_i = \sum_{j} P_{ij}$$

$$= 2\sum_{i} p_i a_i \alpha_i / w \text{ by (2)}$$

$$= v/w \text{ by (4)}.$$

Thus the partial change in the mean fitness $w$ due to changes in the genotypic frequencies $P_{ij}$ from one generation to the next is exactly equal to $v/w$. Ewens (1989) makes detailed comments on the mathematical idiosyncracy of computing $\delta w$ whilst holding $w$ constant on the right-hand side.

(Readers unfamiliar with the elementary mathematics of the least squares fit of a linear model should minimize the residual sum of squares for themselves and prove that the variance removed by the fitted regression is the genic variance as given above. The remainder of the results can be made to follow in a variety of different ways. FMG pp. 12–16 may be helpful, but note that the treatment there is only for the special case of a population in Hardy–Weinberg equilibrium.)

If fitnesses are standardized so that $w = 1$ then $\delta w = v$, and if we take a generation to be the unit of time, then we may present our modern interpretation of the Fundamental Theorem in words as

The rate of increase in the mean fitness of any organism at any time ascribable to natural selection acting through changes in gene frequencies is exactly equal to its genic variance in fitness at that time.

This is as close as I can get to Fisher's wording (1930, 1958) whilst following the interpretation of Price and Ewens. 'Genic' has replaced 'genetic' for the reasons given in Section II and 'mean fitness' has replaced 'fitness of any organism'; these are uncontroversial rewordings (Fisher himself wrote of 'the average fitness' in his letter to Sewall Wright dated 19 January 1931; see below). I have added 'ascribable to natural selection acting through changes in gene frequencies' from Fisher's own words:

'ascribable to natural selection' is from his 1941 explanation of the Theorem (p. 57) and '[due to all] changes in gene frequencies' is from the sentence preceding his statement of the Theorem (1930, 1958), modified as suggested by Price. Price and Ewens repeatedly emphasize that Fisher thought of the immediate effect of natural selection as being only through the changes in gene frequencies. For the sake of minimizing the changes I have kept Fisher's word 'organism', though it would not now be the first choice; in fact Fisher himself replaced it by 'species' in the Summary at the end of Chapter II of *The Genetical Theory*. 'Population' might now be the preferred word.

Although I have only treated the case of a single locus in this account, Fisher clearly viewed the Fundamental Theorem as making a statement covering all loci contributing to the determination of fitness. Ewens (1989) has supplied the multilocus mathematics.

### IV. FISHER'S OWN VIEW OF HIS THEOREM (1930)

Throughout the rest of his life Fisher made comments which throw light on his own attitude to the Fundamental Theorem, and these will be reviewed below in the course of describing how others saw it, but his comments in the 1930 edition of *The Genetical Theory* (Chapter II: *The Fundamental Theorem of Natural Selection*) need to be considered first. These are best studied in the original, and here I only give a brief summary. Of course, the name of the Theorem itself tells us the great importance that Fisher attached to it, as well as his comment that it 'hold[s] the supreme position among the biological sciences'.

Immediately after his statement of the Theorem Fisher writes 'The rigour of the demonstration requires that the terms employed should be used strictly as defined', which should have served as a warning to those who have supposed that the Theorem is approximate only. Then he considers the impact of finite population size on the genic variance for the special case of a random-mating population, making the important statement that with random mating the average excess $a$ and the average effect $\alpha$ are equal.

Next Fisher likens the Fundamental Theorem to the second law of thermodynamics in some important respects, especially that 'each requires the constant increase of a measurable quantity, in the one case the entropy of a physical system and in the other the fitness, measured by $m$, of a biological population'. The $m$ refers to 'The Malthusian parameter of population increase' which Fisher had introduced in an earlier section of the chapter (II) on the Fundamental Theorem and which, as he explicitly recognized, could be negative as well as positive. It seems that he was here carried away by his enthusiasm, but the qualification follows quickly amongst a list of 'profound differences': '(3) Fitness may be increased or decreased by changes in the environment...'. Moreover, '(4) Entropy changes are exceptional in the physical world in being irreversible, while irreversible evolutionary changes form no exception among biological phenomena'. 'Finally, (5) entropy changes lead to a progressive disorganization of the physical world...while evolutionary changes are generally recognized as producing progressively higher organization in the organic world'. I do not know if this is the first time that such an explicit statement was made.

In making these comparisons Fisher is relying on his training in mathematical physics. He took the Cambridge Mathematical Tripos in 1912 and then spent a year of graduate study in physics under (Sir) James Jeans. He was also influenced by (Sir)

Arthur Eddington's views; he and Eddington had been in communication over a statistical question in 1920 (Fisher, 1920), and Eddington had been a referee of Fisher's 1922(c) classic paper *On the mathematical foundations of theoretical statistics*. In *The Genetical Theory* Fisher quotes Eddington in the law of entropy, as well as quoting him approvingly in the Preface: 'We need scarcely add that the contemplation in natural science of a wider domain than the actual leads to a far better understanding of the actual' (Eddington, 1928).

The remaining sections of Chapter II are entitled *The nature of adaptation*, *Deterioration of the environment*, and *Changes in population*. In the first Fisher gives his well-known geometrical analogy to explain why, when many characters are considered simultaneously, large undirected changes will in all probability be deleterious, whilst in the second and third sections he considers the impact of his approach on the study of population growth. Once again we are reminded that it is a partial change in mean fitness to which the Theorem applies:

Against the action of Natural Selection in constantly increasing the [mean] fitness of every organism, at a rate equal to the [genic] variance in fitness which that population maintains, is to be set off the very considerable item of the deterioration of its inorganic and organic environment. It is only if the former of these agencies exceeds the latter that there can be any actual increase in population, while in the reverse case the population will certainly decrease.

### V. SEWALL WRIGHT'S VIEW OF THE THEOREM

The American evolutionary biologist Sewall Wright was a contemporary of Fisher's, born just two months before him, and by 1930 had established himself as a leading figure. In 1922 he had invented the inbreeding coefficient and path coefficients and in 1929 he and Fisher had had an exchange in the *American Naturalist* on the theory of dominance (see Provine, 1986). They had met for the first time in 1924 (Bennett, 1983). From June 1929 until June 1931 they were in friendly correspondence (printed in part in Bennett, 1983, and almost in its entirety in Provine, 1986), initially in connection with the evolution of dominance but widening into a more general discussion, especially after Wright had sent Fisher the manuscript of his major paper *Evolution in Mendelian populations* (Wright, 1931) in August 1929.

Fisher arranged for complimentary copies of *The Genetical Theory of Natural Selection* to be sent to a number of American scientists, including Wright, who also received a review copy from the *Journal of Heredity*. The long review which resulted (Wright, 1930) was the only major one the book was to receive in the United States (Bennett, 1983). In his accompanying letter to Wright, Fisher commented (19 March 1930) 'In some ways the first chapter is the most important, and in some the second'. Wright thanked him on 10 June: 'I wish to thank you very much for sending me a copy of your recent book. I have found it extremely interesting and stimulating'. He does not mention the Fundamental Theorem in this letter or the subsequent one, but he does so in his review.

Wright's review of *The Genetical Theory* is eight pages long. 'It is a book which is certain to take rank as one of the major contributions to the theory of evolution'. Then: 'The core of Dr Fisher's theory of selection is given in Chapter II. He reaches a formula on which he lays great emphasis as "the fundamental theorem of natural selection".'

One's first impression is that the genetic variance in fitness must in general be large and that hence if the theorem is correct the rate of advance must be rapid. As Dr Fisher insists, however, the statement must be considered in connection with the precise definition which he gives of the terms. He uses "genetic variance" in a special sense [i.e. the genic variance].

Wright had thus understood the importance of the genic variance, but he went on, in the review, to remark that the Fundamental Theorem needed revision in order to incorporate dominance, epistasis, and mutation. He, like many others in the next forty-two years, had not taken Fisher's point in full, but, more than any of his contemporaries, he had studied *The Genetical Theory* with care.

Fisher expressed delight with the review when he wrote on 19 January 1931, but added:

I had not intended to take up any special point in this letter, but I am tempted to mention this one, 'The formula itself seems to need revision...'. The point here is that the average fitness is continually being increased by selection, at exactly the same rate as it is being decreased by mutation. This cause of deterioration of adaptedness, due to mutations of the organism, is, in my treatment, classed with the parallel deterioration due to changes in the environments.

Fisher added that Wright will find this point emphasized should he 'happen to re-read p. 41' (*Deterioration of the environment*).

Wright replied on 3 February: 'I was very glad to hear that you were pleased with my review', and

I am very sorry that I overlooked your treatment of mutations on page 41. The essential difficulty which I felt with your conclusions on pages 34–37 still remains, but I should have worded it differently.... I assumed that all internal factors... were intended to be taken into account. I do not know how I managed to overlook your clear statement to the contrary on page 41. I think that if the theorem on page 35 had been stated with its qualifications: "The rate of increase in fitness of any population at any time is equal to its genetic [genic] variance in fitness at that time, except as affected by mutation, migration, change of environment and the effects of random sampling," I would not have been confused by the discussion in the following pages.

This was indeed a noble effort to understand Fisher's obscure theorem, but since it did not include a qualification equivalent to 'ascribable to natural selection acting through changes in gene frequencies' it was not what Fisher had meant. Wright's interpretation was that the theorem was true in respect of total fitness, not partial fitness, provided mutation and other factors were not taken into account.

In 1939 Wright published a short monograph *Statistical Genetics in relation to Evolution* (Wright, 1939) in which he did not mention the Fundamental Theorem explicitly, and in his much larger *The Theory of Gene Frequencies* (Wright, 1969) it only rated a passing reference (p. 121). In 1955, however, he was clear that 'Fisher's formula is more general [than his own] in that it does not involve the assumption of random combination within and among loci (long continued random mating) which we have made' and that 'Fisher's form of statement indicates that it is intended to apply only momentarily rather than to define "fitness" as a quantity that governs the course of evolution, analogously to a potential function'.

Yet from a few remarks in 1988 (see below; Wright 1988) it might seem that he never changed his view of the theorem after all, for he then revealed that he still thought that the assumption of panmixia was basic to its derivation.

VI. THE RISE AND FALL OF THE ADAPTIVE TOPOGRAPHY

Wright may have been the first to misunderstand the nuances of the Fundamental Theorem, but he was certainly not to be the last. The irony is that although he came closer to divining Fisher's meaning than anyone else was to do for many years, and certainly made a much greater effort, his misinterpretation led him to develop the concept of an adaptive topography, which was to foster further misunderstandings in due course. For his letter of 3 February 1931 continued, after a few intervening lines:

Some aspects of the ideas which I tried to express in pages 353 to 355 of my review might be visualised as follows: Think of the field of visible joint frequencies of all genes as spread out in a multidimensional space. Add another dimension measuring degree of fitness. The field would be very humpy in relation to the latter because of epistatic relations, groups of mutations which were deleterious individually producing a harmonious result in combination.

The letter contains a drawing of a continuous line with three humps of different height (fitness) followed by a description of how a species might be seen to evolve in this representation. It would 'tend to move steadily' up the slope towards the nearest maximum 'under the influence of selection' but if this maximum was not the absolute maximum the species would only be able to escape from it and make further progress in fitness through 'something other than the steady pressure of selection'. Wright suggested four factors, (1) a changing environment would continually change the system of humps, (2) new mutations would add further dimensions to the field, allowing new paths of advance, (3) random genetic drift in a small species would allow stochastic jumps from one hump to another, as would (4) a subdivided large species. Wright's image was that of a potential function expressing the selective effect, accompanied by stochastic variation: in modern computer jargon, he has invented 'simulated annealing'.

The image of a 'field of joint frequencies of all genes spread out in a multidimensional space' will not have been new to Fisher, for in November 1930 he had received a letter from J. B. S. Haldane in Cambridge, written on the 9th, which said:

I have ... got a paper on the 2-gene [i.e. 2-locus] case, showing that in the case of dominance when $AB$ and $aabb$ are more viable than $Abb$ or $aaB$ there is no stable equilibrium apart from homozygosis. In this case if we plot the proportion of recessive genes we get trajectories like: [here follows a diagram] representing the change in the composition of the population. The general case of $m$ genes and several ($> 2$) stable equilibria involves problems in $m$-dimensional analysis situs which are too much for me. If heterozygotes have a pull as such we may get stable equilibria of another type, but these may not be stable in the long run, allowing for the appearance of modifiers, as you point out.

The diagram in the letter is identical to the one which eventually appeared in the paper (Haldane, 1931a; reproduced in Haldane 1932, 1966, 1990) except for the labelling. Although Bennett (1983) published the first paragraph of this short letter, he omitted the second, which is published here for the first time with the permission of the Barr-Smith Library of the University of Adelaide.

Thus within the span of three months Fisher had received letters describing multidimensional gene-frequency spaces, first from Haldane and then from Wright. Now Fisher was already famous in statistics for the facility with which he used mathematical arguments in multidimensional space, first displayed in his derivation of the distribution of the correlation coefficient (Fisher, 1915): 'The problem of the frequency distribution of the correlation coefficient $r$, derived from a sample of $n$ pairs,

taken at random from an infinite population, may be solved, when that population can be represented by a normal surface, with the aid of certain very general conceptions derived from the geometry of $n$ dimensional space'. No one was better placed than Fisher, who had had a distinguished undergraduate mathematical career at Cambridge, to understand why untutored excursions into hyperspace were likely to be misleading. Fisher cautioned Wright in his letter of 31 May 1931:

Your letter of February 3rd contains a point about non-optimal points of genetic stability which I should like to take up with you. In one dimension, a curve gives a series of alternate maxima and minima, but in two dimensions two inequalities must be satisfied for a true maximum, and I suppose that only about one fourth of the stationary points would satisfy both. Roughly I would guess that with $n$ factors only $2^{-n}$ of the stationary points would be stable for all types of displacement, and any new mutation will have half a chance of destroying the stability.

When Wright replied on 5 June he mentioned that he had received an offprint of Haldane's paper, and on Fisher's point he commented '$2^{1000}$ is an infinity of such a high order that the maxima may be very widely scattered and still permit a practically infinite number of them'.

Fisher, who was spending the summer at Ames, Iowa, visited Wright in Chicago at the end of June. In later life Wright could recall little of their discussions (Provine, 1986); all we have to go on is the thank-you note from Fisher:

This is just a note to thank you and Mrs Wright for your kindness and hospitality to me in Chicago. I wish I could better understand your view on those points on which I differ from you, but on the points I have discussed with Lush [J. L. Lush of Iowa State College, Ames], I see little chance that I shall ever do so. However, there is a substantial body of theory on which I think we do agree and that after all is of infinitely more interest to the world at large than the very obscure points still in dispute.

It is easy to surmise that Wright's enthusiasm for his image of an adaptive topography, based on his deep biological knowledge and intuition, came up against the rapier-like quality of Fisher's analytical mind, trained in mathematics and mathematical physics and thus thoroughly familiar with the geometry of $n$-dimensional Euclidean space and potential theory. I conjecture that the very obscure points still in dispute were about $n$-dimensional surfaces. This appears to have been the last letter between Fisher and Wright.

Wright's image of an adaptive topography proved to be compulsive viewing, and came to dominate thinking in evolutionary biology for a long time. Confusingly, however, in his first publication on it (Wright, 1932) he departed from the mental picture of a multidimensional field of gene frequencies which he had described in his letter to Fisher and instead described a field of gene combinations: 'If the entire field of possible gene combinations be graded with respect to adaptive value under a particular set of conditions, what would be its nature?' In this new image, a point in the space represented a particular gene combination, not a particular set of gene frequencies, though fitness (adaptive value) was still added in a further dimension as previously. A species was no longer characterized by a point representing its gene frequencies, but by a cluster of points representing the individuals, a sort of bounded cloud. Wright then based his evolutionary arguments on a two-dimensional drawing of

this multidimensional space, with the third dimension, for fitness, represented by contours as on a map. 'A species whose individuals are clustered about some combination other than the highest would move up the steepest gradient toward the peak', as if fitness were a potential function. Wright then drew the same conclusions about the importance of random genetic drift from his new analogical image as he had from the old.

Setting aside for a moment the question of whether the properties of the multidimensional space could really be thought about in only three dimensions, Wright's new model is severely restricted by being *haploid*. It is based on *gene combinations*, that is to say, *haplotypes* in modern terminology. Even in as many dimensions as there are loci, a point represents not an individual, as Wright asserts, but half an individual. Yet there is no doubt that he is thinking about diploid individuals, for the opening sentence of his paper is 'The enormous importance of bi-parental reproduction as a factor in evolution was brought about a good many years ago by East' and then, immediately before introducing 'the field of possible gene combinations', 'There is no difficulty in accounting for the probable uniqueness of each individual human being or other organism which is the product of biparental reproduction'. It is to the haplotype that Wright attaches a fitness, not an individual. It is (to paraphrase Dawkins, 1976) the *selfish haplotype* which flourishes on Wright's metaphorical mountains. Consequently the model cannot take into account dominance in fitness, which was precisely the phenomenon which Fisher struggled successfully to allow for in the Fundamental Theorem.

Returning to the question of the two-dimensional representation of a multidimensional space, Wright's diagrams showing 'The combinations of from 2 to 5 paired allelomorphs' are technically *Boolean cubes* for from 2 to 5 factors, starting with the square (2 factors) and cube (3); in his 'diagrammatic representation of the field of gene combinations in two dimensions instead of many thousands', 'it is assumed that the genotypes are packed, side by side, in a two dimensional space in such a way that each is surrounded by genotypes that differ by only one gene replacement' (Wright, 1988). Now there is a fundamental mathematical reason why one cannot represent a Boolean cube in two dimensions so that all adjacent corners in $n$ dimensions are adjacent to each other in the two dimensions. The reason is to do with the structure of a Venn diagram for $n$ sets.

Each of the $2^n$ segments of an $n$-set Venn diagram corresponds logically to each of the $2^n$ corners of an $n$-dimensional Boolean cube, and the general importance of Venn diagrams may be said to stem from the fact that they are, in a sense, the best possible 2-dimensional representations of $n$-dimensional Boolean cubes (see, for example, my popular article *How to iron a hypercube*; Edwards, 1991). Wright's two-dimensional field may be thought of as an attempt to construct a Venn diagram for a huge number $n$ of sets. A satisfactory solution to this problem has only recently been found (Edwards, 1989), from which it may be shown that the mean number of segments surrounding a segment (corresponding to Wright's 'genotypes that differ by only one gene replacement') is $4-2^{3-n}$, which tends to 4 as $n$ tends to infinity. In other words the number of immediate neighbours to a corner of a Boolean $n$-cube, which is of course $n$ (corresponding to the $n$ loci, at each of which a single gene substitution may occur) is represented in the best possible two-dimensional version, on average for large $n$, by

just 4. There is absolutely no way in which the proximity structure of a large-dimensioned Boolean cube can be modelled in two dimensions, and any conclusions drawn from the assumption that it can must be treated with reserve. In 1932 Wright did indeed say 'The two dimensions of figure 2 are a very inadequate representation of such a field' (i.e. of 'the entire field of possible gene combinations'), but with the enthusiastic reception of his graphical arguments he threw caution to the wind.

Both Fisher and Haldane were present when Wright gave this paper at the 6th International Congress of Genetics at Cornell in August 1932. There is no record of any discussion, but Fisher will probably have felt that Wright's paper confirmed his own view that excursions into *n*-dimensional space were naive and ushelpful. For his part, Wright will have heard Fisher warn not to expect too much from the application of mathematics to biology, as if Fisher foresaw the dangers into which he thought Wright was drifting:

I believe that no one who is familiar, either with mathematical advances in other fields, or with the range of special biological conditions to be considered, would ever conceive that everything could be summed up in a single mathematical formula, however complex. (Fisher, 1932)

What he may not have foreseen is that T. Dobzhansky was to promote Wright's adaptive topography with such enthusiasm that it captivated a whole generation of evolutionary biologists. 'Many others besides Dobzhansky were much impressed by Wright's 1932 paper' writes Provine (1986). 'His adaptive surface diagrams appeared and reappeared frequently in papers and books and were constantly referenced'.

In 1935 Wright reverted to his original idea of an adaptive topography, the space once again becoming a space of gene frequencies ('cf. Haldane, 1931' he writes) with the addition of a dimension for 'the average adaptive value' which he identifies with the quantity in Fisher's Fundamental Theorem.

If evolution were controlled only by selection, the locus of a population characterised by any given set of gene frequencies would move up the steepest gradient in the field.

Once again Wright introduces the misleading notion of a potential function, this time on the basis of a different graphical representation. Fisher was less than impressed; at a Royal Society meeting on the theory of natural selection the following year he remarked causticly 'It has been proposed ... that the environment, picturesquely renamed the landscape, governs the course of evolutionary change, much as the field of force determines the trajectory of a comet' (Fisher, 1936). In 1949 Wright was to accept that 'steepest ascent' did not apply (Wright, 1949):

With constant genotypic selective values, the species tends to move toward one of the peaks, though not, as carelessly stated previously, up the steepest gradient in the surface $\overline{W}$ from the point at which it is located.

However, this admission that even in the simplest case there was in fact no potential function did nothing to prevent the spread of the contrary belief. The idea that the average adaptive value was a potential function of the gene frequencies which determined gene-frequency changes was to dominate much thinking in evolutionary biology during the next four decades. A single example, from an influential population geneticist addressing a Zoological Congress (Lewontin, 1965), will suffice:

If we then know these [genotype] fitnesses and the frequencies of the different genotypes we can calculate a parameter $\bar{W}$, the average fitness of the population. As the frequencies of the different genotypes change, the average fitness will change... This can be represented in a topographical diagram... [which] shows an "adaptive topography"... By connecting points of equal $\bar{W}$ we get equipotential lines forming a kind of topographic map.

We can now state a fundamental theorem of intrademe evolution. Provided that fitnesses of genotypes are not functions of the commonness or rarity of those genotypes and provided the population is very large in size, then the frequencies of the genotypes [*sic*] in the population will change under natural selection so as to maximise $W$.

As Provine (1986) has related, after 1935 the two versions of an adaptive topography travelled together:

Wright's concept of the surface of selective value has become famous because of its apparently great heuristic value in conveying graphically the relationship between organisms, mechanisms of evolution, and adaptation. Despite its great attractiveness and apparent ease of interpretation, the surface of selective value is one of Wright's most confusing and misunderstood contributions to evolutionary biology. Wright himself has contributed to the confusion.

In the first place, Wright contributed not just one conception of his surface but two very different versions that mathematically were wholly incompatible. Worse, he frequently treated these two incommensurable conceptions as if they were together a unitary conception, and he switched back and forth between them often.

In 1971 I had expressed precisely these views in a paper 'Fisher's Fundamental Theorem of Natural Selection and Wright's Adaptive Topography: a controversy revisited' read at a joint meeting of the Biometric Society and the Royal Statistical Society (Edinburgh Group) (Edwards, 1971 a, abstract only). The paper remains unpublished because it was rejected for publication on more than one occasion. However, at the same time I wrote a long review of Volume 2 of Wright's great work *Evolution and the Genetics of Populations – The Theory of Gene Frequencies* (Wright, 1969) in which, after much detailed discussion of the gene-frequency version of the adaptive topography, I remarked 'The general theory for which Wright seeks is a will-o'-the-wisp' (Edwards, 1971 b). In my book *Foundations of Mathematical Genetics* (1977) I explained the omission from it of

all treatment of gene-frequency change by the use of differentials.... This is a major departure from current text-book practice (see for example Crow and Kimura, 1970; Elandt-Johnson, 1971; and Li, 1976). Wright (1969) gives the fullest account of the treatment, with its associated general 'fitness function'. It may only be a matter of notation, but I believe it to have been the source of misunderstandings to which I refer in my review of Wright's book (Edwards, 1971 b).

Provine's book on Sewall Wright contains no references to these criticisms nor, much more remarkably, to the devastating criticism of the adaptive topography published by Fisher in 1941, to which I now turn.

In 1938 E. B. Ford, of Oxford, sent Fisher the page proofs of his forthcoming book *The Study of Heredity* (Ford, 1938). Fisher read it 'with the greatest pleasure and interest' but wishes 'to take up argumentatively' Ford's statement, on pages 174–5, of the views developed by Sewall Wright: 'either the statement or the original views seem to be confused'. In his letter (2 May) Fisher then clearly distinguishes Wright's two types of adaptive topography, the gene-combinations one and the gene-frequencies one,

and we may be sure that Ford was not able to correct his pages 174–5 before his book went to press, because they do indeed completely confuse the two types by describing the first kind and then arguing as if it were the second.

Fisher was evidently uncertain whether the confusion originated with Wright himself or with Ford, which shows that he had not been following the American developments closely, but he must have been sufficiently interested to follow the matter up, perhaps goaded by the fact that Ford had not amended his book and by an essay of Wright's in *The New Systematics* (Wright, 1940). The result was his second publication on the Fundamental Theorem (Fisher, 1941) in which, with startling clarity, he drew attention to Wright's confusion:

> Wright's conception...that selective intensities are derivable, like forces in a conservative system, from a simple potential function dependent on the gene ratios as a whole, has led him into extensive but untenable speculations. For example, in the New Systematics, p. 170 [Wright, 1940], we find: 'As already noted, $\overline{W}$ [the mean fitness] is a function of all gene frequencies. In the practically infinite field of gene combinations, possible from differences in only a few thousands, or even hundreds of loci, there are likely to be an enormous number of different harmonious combinations of characters. These would appear as peak values of $\overline{W}$, separated by valleys or saddles in a multidimensional surface'.
>
> Prof. Wright here confuses the number of genotypes, e.g. $3^{1000}$, which may be distinguished among individuals, with the continuous field of variation of gene frequencies. Even if a potential function, such as $\overline{W}$ is supposed to be, really existed, the large number of genotypes supplies no reason for thinking that even one peak, maximal for variations of *all* gene ratios should occur in this field of variation.

Fisher ended his 1941 paper with a fully-worked numerical example of 'a model involving powerful selection, in which the fitness of the species as a whole, judged by external criteria is entirely inoperative'. Many years later, as we shall see, others were to exhibit models in which the mean fitness did not increase, but, with supreme irony, these were held to be counterexamples to Fisher's Fundamental Theorem rather than to Wright's adaptive topopgraphy. Fisher went on to make one or two other comments on the concept of an adaptive topography in 1958 (see the next Section, and Edwards, 1990).

In 1988 Wright, well-advanced in years, chose to defend himself against Provine's severe criticism (Wright, 1988), and did so by ignoring the existence of the gene-frequency-based adaptive topography altogether, thus deflecting Provine's remarks on the incompatibility of the two versions. Against Provine's extensive mathematical criticism of the 'gene-combinations' adaptive topography Wright offered no defence, preferring to concentrate on defending his 'shifting-balance' theory of evolution verbally as opposed to graphically. But Provine (and I) had not argued that the theory was wrong; only that the graphical metaphor was inappropriate. Wright had defended the defensible but ignored the criticism. As to my own criticisms of the gene-frequency-based adaptive topography mentioned above (Edwards, 1971*b*), Wright did not respond, though I know he read the review because J. F. Crow informed me privately at the time that he had not been upset by it, for which I am grateful. P. A. P. Moran (author of Moran, 1962, 1964) wrote to me in 1974 'I was very interested in your review of Wright in Heredity which I had missed. I thoroughly agree with it'.

It was only human of Wright to have basked in the enthusiasm with which his 1932 diagrams were adopted by population biologists who were not technically competent to

see their mathematical naivety, but it was strange that the metaphor was powerful enough to ensure that even the criticism of Fisher (1941) had no impact. In 1988 Wright pleaded that 'The concept of "surfaces of selective value" was introduced in 1932 merely in connection with a nonmathematical comparison of elementary evolutionary processes' and suggested that Provine 'was looking for something more mathematical than was intended'. To hold that view one would have to ignore both the gene-frequency surface of selective value and Wright's many papers on the topic after 1932, which is what Wright did, for in 1988 he referred to nothing between then and 1977.

### VII. J. B. S. HALDANE AND THE THEOREM

Bennett (1983) has described the British reception of *The Genetical Theory*. It seems that no one noticed the Fundamental Theorem, not even Haldane. In a letter dated 17 December 1930 Fisher expressed his disappointment that Haldane was not to review the book in the *Eugenics Review*, and wondered whether even so Haldane would allow what he had already written to appear later. But Haldane had lost his manuscript, to Fisher's distress: 'I should greatly have liked to read it'. Happily, a couple of months later it turned up and Haldane sent it to Fisher, who found it 'extremely interesting'. It was subsequently published as an 'essay-review' under the title 'Mathematical Darwinism' (Haldane, 1931 b).

The book before us is of the latter class [books which, though often inaccurate in detail, state a new point of view, and lay the foundations of new branches of science]. It is extremely difficult and highly controversial. ... No serious future discussion either of evolution or eugenics can possibly ignore it.

Haldane did not mention the Fundamental Theorem explicitly either in this essay or in his review in the *Mathematical Gazette* (Haldane, 1931 c).

Haldane's own book *The Causes of Evolution* came out in 1932 (Haldane, 1932, 1966, 1990). In the Introduction he referred to *The Genetical Theory* as 'a brilliant book', a compliment which Fisher returned in his own unpublished review of *The Causes of Evolution* (since published by Bennett, 1983). However, Haldane 'ignored the theorem' in his book (the expression is from Leigh, 1990), and I am not aware that he ever alluded to it, though he did embrace the adaptive topography at least as a metaphor: 'A large population of any given composition will inevitably evolve towards one particular maximum of $W$' (Haldane, 1958).

The 'official' review which the *Eugenics Review* commissioned was contributed by C. G. Darwin (1930), brother of Leonard, who similarly made no mention of the theorem.

### VIII. 1955–72: THE THEOREM MISUNDERSTOOD

For twenty-five years after its publication the Fundamental Theorem had no impact on the literature other than through its influence on Sewall Wright. It seems not to have been noticed by either of the two principal writers on mathematical genetics of the day besides Wright and Haldane, Hogben (1933, 1946) and Dahlberg (1947). But then Hogben and Dahlberg were more interested in genetical statistics than evolution. More remarkably, Ford (1938) does not mention it, even though, as we saw in Section II, he was Fisher's co-author (Fisher & Ford, 1926, 1928) when the germ of the idea was first published. Malécot's *Les mathématiques de l'hérédité* (1948; English translation 1969) is silent on the theorem. But in 1955 Li's *Population Genetics* appeared and remained the

principal text until Moran (1962), Ewens (1969a), Jacquard (1970), and Crow & Kimura (1970). As mentioned in Section I, Li produced a theorem which he claimed was 'a simplified version of Fisher's *fundamental theorem of natural selection*', though he did not specify in what respect it was simplified.

Li's theorem was the growth-rate theorem of Section I applied to genotypes, and it is indeed true that the mean fitness of the genotypes in a particular generation is increased through the action of selection by an amount precisely equal to the *genotypic* variance in fitness, if we standardize the fitnesses so that the mean is unity before selection acts. But Li claimed that 'As the individuals with low viability will be relatively less numerous after the operation of selection than before it, so the *average* fitness of the selected population will be higher than that of the preceding generation'. This does not follow, because the preceding generation and the present one are separated by mating, which ensures that in general the genotypic frequencies amongst the young are not the same as those amongst their parents. In his review of Li's book Bennett (1956) remarked:

...the author makes a very serious error as the result of confusing genotypic with genetic variance. In what he claims is a simplified version of Fisher's fundamental theorem of natural selection, he asserts that the increase in the average selective value of the population per generation is equal to what is, in fact, the genotypic variance of the selective value.

Li's terminology was indeed unfortunate, for in his book he used 'genetic variance' in Fisher's original sense (now 'genic variance') but called the genotypic variance the 'actual genetic variance', thus inadequately separating the two notions. Bennett's review, however, had no effect on the subsequent literature. The only non-trivial case where the round of mating has no effect on the mean fitness is when fitness is exactly determined by the genes acting multiplicatively, and the population is mating at random, for then it will be in Hardy–Weinberg equilibrium both before and after mating.

In the same year as Li's book appeared, Crow (1955) discussed the theorem, and concerted attempts to understand it soon followed. Crow & Kimura (1956) and Kempthorne (1957) struggled to come to terms with Fisher (1941), but misinterpreted Fisher's 'simple example' (which had been only intended to demonstrate that the average effect and the average excess need not be the same) as leading to an additional condition required for the truth of the theorem.

[As a critic enjoying the advantage of having read Price (1972) I may seem harsh in my assessment of those who wrote before Price, but I can mete out similar treatment to my own 1967/68 typescript *On the Fundamental Theorem of Natural Selection* referred to by Turner (1970), which contained the same mistake. Because of my doubts, however, it was never published, and on reading Price I scribbled on it 'nb this is mostly nonsense – 2 Apr 73' (Edwards, 1990). But a brief note in *Nature* (Edwards, 1967) revealed my mistake.]

Fisher had examined a case of non-random mating in which departure from Hardy–Weinberg equilibrium was measured by a parameter $\lambda$:

If $\lambda$ remains constant the actual change in the mean or total measurement in constant environment will be that due to change of gene ratio [frequency] only.... If, in fact, the value of $\lambda$ changes, the change in the population mean will differ from that ascribable merely to the change in gene ratio, ....

But as he had intended the Theorem to refer only to this 'change in the population mean ascribable merely to the change in gene ratio', a changing value of $\lambda$ did not invalidate it, and constancy of $\lambda$ was not an additional condition as Crow, Kimura and Kempthorne had concluded.

Kempthorne had corresponded with Fisher on just this point two years earlier, sending him a typescript which had prompted Fisher to reply (31 January 1955; Bennett, 1983) 'I do not at all agree with the last sentence of the opening paragraph of your introduction, "later in 1941 Fisher showed that this is true only if the quantity [$\lambda$] remains constant"', and he gave his reasons at length. Again, on 18 February, Fisher had written 'I should be entirely satisfied if you cared to use the two quotations from page 56 of my 1941 paper, which seemed to express just what I mean' (I believe these to encompass the quotation above), and 'the only evolutionary effect, either in increased fitness or in anything else, that I can recognize as such, is constituted by the changes in gene ratio'. But Kempthorne was unmoved, and included the apparent condition in his account of the Theorem in his book (1957), covering himself by commenting 'I have found Fisher (1930, 1941) entirely obscure with regard to the derivation of the result'.

In fact Fisher, Kempthorne, and Kimura were engaged in a three-way correspondence about the Fundamental Theorem in 1955–56 (Kempthorne, 1957; Bennett, 1983; Edwards, 1990), for Kimura had also sent Fisher the draft of a paper, which eventually appeared as Kimura (1958). In this paper Kimura obtained a very general formula for the total change in mean fitness for the continuous-time model which he considered to be a 'reformulation of the results published by Fisher in 1930 under the title *The Fundamental Theorem of Natural Selection*, and in no way differs from it in substance'. Mathematically Kimura's result was indeed true, but since it treated the total change in mean fitness, and not the partial change, it was not really Fisher's theorem: it differed from it by the addition of two equal components, one to each side of the equation, thus obscuring Fisher's intention (Ewens, 1989). Moran (1962) in his book the *Statistical Processes of Evolutionary Theory* did not mention the Fundamental Theorem by name, but followed essentially the treatment by Kimura (1958).

Kimura went on to enunciate his related 'Maximum principle in the genetical theory of natural selection', according to which it should be possible to derive the changes in gene frequencies just as the laws of motion can be derived from the principle of least action in physics. I have given my reasons elsewhere for thinking that, on the contrary, it 'simply reflects a feature of the mathematical structure, but adds nothing to an understanding of that structure' (Edwards, 1974; 1977).

The attempts of Crow & Kimura (1956) and Kimura (1958) to interpret the Fundamental Theorem, coupled with Wright's occasional references to it (e.g. Wright, 1955), had an undesirable side-effect in that the theorem began to acquire a wider audience without its true nature having been elucidated. Consequently its name came to be used rather loosely for the notion of increasing mean fitness, on the basis of Fisher's wording of the theorem taken without consideration of all his qualifying statements. Thus a widely-read paper by Kojima & Kelleher (1960) opened as follows:

In 1930 R. A. Fisher formulated the fundamental theorem of natural selection which states that "the rate of increase in (mean) fitness of any organism at any time is equal to its genetic variance in fitness at that time" (Fisher 1930). Later, some modifications and variations of this

theorem were considered by Wright (1949, 1955), Crow and Kimura (1956) and Kimura (1958) in attempts to interpret the theorem over wider genetic circumstances.

When the members of a population are mating at random and their fitness values do not vary over time, Fisher's theorem is usually understood to imply that the mean fitness will always increase with time and that this increase is equal to the additive genetic variance in fitness.

There was, however, nothing in Kimura's paper to support such an interpretation unless one ignored everything except the additive effects of the genes.

In another widely-quoted paper from the same year Lewontin & White (1960), treating the case of two loci by Wright's adaptive topography without mentioning the Fundamental Theorem, wrote:

If the fitnesses of the various genotypes are constants and do not depend upon the frequencies of the genotypes, it can be demonstrated that the gene frequencies will change in such a way as to increase the value of $\overline{W}$. That is, the population will tend to "ascend" the slopes of the topography, coming to rest on a "peak".

This prompted Moran (1964) to write a paper entitled *On the nonexistence of adaptive topographies* in which he demonstrated that the mean fitness did not necessarily increase in the two-locus model and concluded that 'Wright's conception of an 'adaptive topography' is untenable'.

The 1960 papers of Kojima & Kelleher and Lewontin & White are good examples of the uncertainty which at that time surrounded the distinction between Fisher's formulation and Wright's, for the first pair of authors were using Fisher's terminology and the second pair Wright's. This was all the more remarkable because Lewontin and Kojima were in communication at the time, being joint authors of another paper (Lewontin & Kojima, 1960) in which they wrote 'These mean adaptive values may then be put in the form of adaptive topography, a concept introduced by Wright (1932)'. (In fact, as we saw in Section VI, Wright introduced the gene-frequency adaptive topography in 1935, not 1932.)

The uncertainty was also evident in Kimura's (1965) response to Moran (1964), in which he showed that subject to the side condition of unchanging Robbins coefficient of linkage disequilibrium the mean fitness increased: Kimura mentioned Wright when considering the equilibria and Fisher when considering the increase of mean fitness.

As a result of these developments the wheel turned full circle and the name of Fisher's Theorem became attached to the idea of increasing mean fitness in the discrete-generation model. Thus Ewens (1969b) opened his *A generalized fundamental theorem of natural selection* as follows:

A classical result (Fisher 1930) of population genetics is that if, in a random-mating population, the fitness of any individual depends on his genetic constitution at a *single* locus, then the mean fitness of that population increases (or at worst remains stable) with time. This is true for an arbitrary number of alleles at the locus and for arbitrary fitness values; (for the best proof of this theorem see Kingman 1961).

Ewens was here quoting Fisher (1930) in connection with a theorem about increasing mean viability at a single multi-allelic locus in the discrete-generation model, which was not proved until 1959, as we shall see in the next section. He went on 'Unfortunately, if it is supposed that fitness depends on the genetic constitution at two loci, Fisher's result no longer holds (Moran 1964)', though what Moran had actually claimed to have

demonstrated was that 'Wright's conception' of an adaptive topography was untenable; he had not mentioned Fisher's Theorem.

A consequence of this shift in terminology was that when other writers began to contribute to the literature they inherited a false certainty about the theorem. Thus Karlin & Feldman (1970a), writing about the two-locus model, had no doubt what the theorem was:

[The Fundamental Theorem of Natural Selection] states that when, in a random mating population, the fitness of any individual depends on his genotype at a single locus then the mean fitness of the population increases from generation to generation with constancy occurring only at the equilibria of the gene frequencies.

Moreover, after making some remarks about attempts to find conditions under which this 'theorem' might be true for two loci, these authors wrote (Karlin & Feldman, 1970b) 'it appears that these attempts to save the fundamental theorem are quite pointless'. Many other instances of the misappropriation of the name of Fisher's theorem for something that, though related in a way not then clearly understood, was certainly different, may be found in Volume 1 of *Theoretical Population Biology* (1970).

Whilst these developments prompted by consideration of the two-locus model were taking place, Li had by 1967(a, b) come to regard the Fundamental Theorem for a discrete-generation model as asserting that the mean fitness (standardized) would increase by an amount equal to the genic variance, and he considered any departure from this as vitiating the theorem. Thus in the case of a single locus with two alleles 'Fisher's theorem, if applied to discrete-generation model, is true only when the three [genotypic] fitness values are additive' (Li, 1967a). In the only piece I have hitherto published on the Fundamental Theorem (Edwards, 1967) I protested uncertainly and ineffectively.

1969 and 1970 saw the publication of three major textbooks in mathematical genetics, Ewens's (1969a) *Population Genetics*, Jacquard's (1970) *Structures génétiques des populations*, and Crow & Kimura's (1970) *An Introduction to Population Genetics Theory*.

Chapter 3 of Ewens (1969a) was entitled *The Fundamental Theorem of Natural Selection*, and discussed the properties of the mean fitness for the standard discrete-generation model. Not until the last section was the Fundamental Theorem itself mentioned:

The results of the previous sections indicate that the fitness of any population will usually increase, the rate of increase bearing a close relationship to the additive part of the genetic variance. Such a result has been called (Fisher, 1930) the 'Fundamental Theorem of Natural Selection', and has had considerable influence.

It is interesting to see how Ewens, who twenty years later was to explain Price's interpretations of the Theorem so clearly (Ewens, 1989), is here cautious in his choice of words, a caution that was to evaporate by the time of his next book (Ewens, 1979; see below).

Jacquard (1970) arrived at the 'Fundamental Theorem' by missing the second-order term in his account of the change in mean fitness at a multiallelic locus assuming random mating, as I pointed out in my review (Edwards, 1972a); in the English edition (Jacquard, 1974) the error was corrected and the Fundamental Theorem considered to be an approximation only.

Crow and Kimura's (1970) textbook naturally relied heavily on their earlier papers described above. They too showed caution in discussing Fisher's precise meaning (having found his treatment 'recondite'), but they did not make the advance in interpretations involving partial fitness which Price was to make two years later.

A fourth major textbook of the era was Elandt-Johnson's (1971) *Probability Models and Statistical Methods in Genetics* which, though it concentrated more on statistics than evolution, ventured a formal statement of the Fundamental Theorem:

THEOREM. If a population satisfies conditions (10.18) [one locus, multiple alleles, constant fitnesses, random mating, discrete generations], and additionally the fitnesses of the genotypes ... are additive functions of the genes ..., then the rate of increase in mean fitness per generation is proportional to the additive genetic variance with respect to fitness.

This corresponded to Li's view described above; in my review (Edwards, 1972b) I protested at Elandt-Johnson's 'misappropriation of the name [of the Fundamental Theorem]' and added for good measure that this was 'an unfortunate characteristic of much modern writing in mathematical genetics'.

Thus in the decade 1960–70 the name 'Fundamental Theorem of Natural Selection' was usually used for a false 'theorem' which had grown out of Wright's concept of an adaptive topography but which the literature now associated with the name of Fisher, whose reputation was thereby adversely affected. Fisher died in 1962, and his last published comment on the matter was one of protest (Fisher, 1958a; see Edwards 1990):

I have never indeed written about $\overline{W}$ and its relationships, and now that the alleged relationship has been brought to my attention, I must point out that the existence of such a "potential function" as that which Wright designates by $\overline{W}$, is not a general property of natural populations, but arises only from the special and restricted cases which Wright has chosen to consider. Selective tendencies are not, in general, analogous to what mechanicians describe as a conservative system of forces. To assume this property is one of the gravest faults of Wright's formulation.

But his protest, like the earlier one (1941), was in vain, and mathematical geneticists impressed by the discovery of fresh examples in which the mean fitness did not increase held them against 'the Fundamental Theorem' in spite of the fact that the first such example had been constructed by Fisher himself (1941) for the specific purpose of criticizing Wright's idea of an adaptive topography (see above). Sometimes, however, as in the quotation from Elandt-Johnson above, the name 'Fundamental Theorem' was used solely for the case of additive fitnesses, a theorem which at least had the virtue of being true even if very restricted.

As already mentioned in Section VI, in a paper delivered in 1971 (Edwards, 1971a; abstract only) I tried at least to disentangle the adaptive topography and the Fundamental Theorem, but it was a Herculean task in the absence of a clear understanding of the latter. That understanding was not available until Price (1972).

Perhaps the last major account of the theorem which did not have the possibility of relying on Price was that of Turner (1970). In a review *Changes in mean fitness under natural selection* he took Li's 1967 view about when the Theorem was exact, and regarded Kimura's (1958) treatment of the Theorem as 'brilliant' since it 'eliminates the flaws in Fisher's theorem' ('which is lacking mathematical rigour and [in which] the concept of fitness is hazy'). But at least Turner's last words were accurate:

The simple view of evolution that mean fitness will increase because the less fit genotypes die is not adequate because sexual reproduction shuffles the genes and the fitnesses of genotypes may change with changes in the population.

Since this was just the difficulty Fisher had intended his Fundamental Theorem to surmount forty years earlier, there was still room for progress.

With the advantage of hindsight we can now see that it should perhaps have been obvious that if (1) the Fundamental Theorem was exact, (2) the definition of genic variance on the 'right-hand side' of the theorem was not in dispute, and (3) the total increase in mean fitness (the 'left-hand side') in the simplest discrete models did not exactly equal the genic variance in general, then Fisher could not have meant the left-hand side to refer to the total increase in mean fitness. Perhaps it was the force of this logic which persuaded Price of the truth of the theorem (he does not relate), in which case he succeeded where so many had failed because he was the first to combine adequate technique with an absolute confidence that Fisher was, in some sense worth capturing, correct.

### IX. INCREASING MEAN FITNESS IN A MULTIALLELIC MODEL

Whilst Crow, Kimura, and Kempthorne in the United States were making the attempts to understand the Fundamental Theorem described in the last section, a separate development stemming from the theorem was taking place in Fisher's Department of Genetics at Cambridge University (see Edwards, 1990).

Owen (1954), a colleague of Fisher's, had considered the conditions for equilibrium in the discrete-generation, random-mating, three-allele model, and his graduate student Mandel together with a fellow-student Hughes (Mandel & Hughes, 1958) conjectured that for an arbitrary number of alleles 'the mean viability [fitness] increases each time the population undergoes the process of mating, but to prove this statement generally appears to be a matter of considerable mathematical difficulty'. (Their mathematics shows that they really meant 'increases each generation' and not just as a result of mating.) They were only able to prove the result for gene frequencies arbitrarily close to an equilibrium state. They held that the Fundamental Theorem did not constitute a proof since 'its derivation depends on a continuous time argument' (but see Ewens, 1989).

I have related the history of the proof of the conjecture elsewhere (Edwards, 1977, Section 4.8). In brief, the conjecture was stated to be true by Mandel (1959) and proved by Scheuer & Mandel (1959). Simultaneously it was under consideration by Mulholland & Smith (1959), a proof being obtained by Mulholland, and in the following year a third independent proof was supplied by Atkinson, Watterson & Moran (1960). Subsequently a simplified proof was given by Kingman (1961), a matrix formulation of which will be found in Edwards (1977).

None of these authors supposed that the result constituted a proof of the Fundamental Theorem, and Kingman in his definitive account did not even mention the Theorem. Nor was there any anticipation that a result so difficult to prove could be extended to more complex models.

There is unfortunately no record of any comment by Fisher on precisely how this work related to his Fundamental Theorem (Edwards, 1990); in 1971 Owen was

adopting the conventional wisdom by using the name of the theorem to refer to straightforward increasing mean fitness (Arunachalam & Owen, 1971).

Li (1969) gave a neat formulation of the total change in the mean fitness at a multiallelie locus under random mating. In the same notation as Section III, he found this to be

$$\Delta w = v/w + \sum_{i,j} \Delta p_i \, \Delta p_j \, w_{ij},$$

thus identifying the difference between the total change $\Delta w$ and the partial change $\delta w$. His derivation will also be found in Edwards (1977).

### X. THE SECOND EDITION OF *THE GENETICAL THEORY* (1958)

The second edition of *The Genetical Theory* was published in 1958 (Fisher, 1958*b*), but Fisher had been thinking about a reprint since 1955 ('I do not like to call it a new edition', he wrote to E. B. Ford on 25 November; Bennett 1983). Price (1972) has described in detail the difficulties introduced in Chapter II through poor editing and proof-correction. The wording of the Fundamental Theorem itself remained unchanged, but Fisher added three paragraphs emphasizing the point about dominance at the end of the section containing the theorem, paragraphs which Wright, incidentally, never remarked on (nor did Price, 1972, though Bennett, 1983, thought it 'should not be overlooked' since it 'explains how, in [the] Fundamental Theorem of Natural Selection, the evolutionary effects ascribable to the dominance component of the genotypic variance are credited to gene substitutions at other loci'):

In addition to the genetic variance of any measurable character there exists, as has been seen, a second element comprised in the total genotypic variance, due to the heterozygote being in general not equal to the means of the two corresponding homozygotes. This component, ascribable to dominance, is also in a sense capable of exerting evolutionary effects....

This indirect and conditional factor in selection seems to have been able to produce effects of considerable importance....

Such effects ascribable to the dominance component of the genotypic variation are not in reality additional to the evolutionary changes accounted for by the fundamental theorem; for in that theorem they are credited to the gene-substitutions needed, for example, to develop bigger or brighter flowers....

### XI. THE RECEPTION OF PRICE'S VIEW OF THE THEOREM (1972)

In this review I have repeatedly referred to G. R. Price's account of the Fundamental Theorem (1972), but at the time it was almost completely ignored. Indeed, from personal knowledge I can only name four people who looked favourably on Price's interpretation prior to Ewens (1989). The first was C. A. B. Smith, the joint editor of the journal *Annals of Human Genetics* in which it was published, whom Price thanks for his help. Smith had just published a related paper with Price (Price & Smith, 1972) whose 'secondary purpose' was 'to prepare the way for an explanation of Fisher's "fundamental theorem" in a future paper'. Professor Smith informs me that he 'half accepted' Price's explanation. The second was J. H. Bennett who wrote (Bennett, 1983) 'In an interesting article... Price came close, I believe, to Fisher's meaning in a number of respects...'. The third was D. S. Falconer, who referred to it in the second edition of his book *Introduction to Quantitative Genetics* (1981) which I discuss below, and the

fourth was me. In April 1973 I wrote to A. Robertson, of Edinburgh, 'After thinking about Price's *Ann. Hum. Genet.* paper I believe we have all been too naive in our interpretations. I now see dimly what Fisher was driving at, and his 1941 paper in particular is at last beginning to make sense'. 'Price has got closer than anyone in divining Fisher's thoughts' I wrote to Ewens in 1976, enclosing a typescript in which I had written that Price's account 'must be the starting point for any future discussion of the theorem' (see Edwards, 1990).

This was not an auspicious start for a reappraisal of the Fundamental Theorem.

For the most part population genetics theory carried on as if nothing had happened. Karlin (1975) continued his earlier use of the name 'Fundamental Theorem' (quoted above in Section VIII from Karlin & Feldman, 1970 *a*), complete with a section entitled 'The Nonvalidity of the Fundamental Theorem of Natural Selection'. Li updated his 1955 book into *First Course in Population Genetics* (Li, 1976) without mentioning Price's paper (though he did refer to other papers in the *Annals of Human Genetics* by Price). His 1967 interpretation of the Fundamental Theorem (see Section VIII) replaced that of 1955. In my *Foundations of Mathematical Genetics* (Edwards, 1977) I declined to discuss the Theorem (see the third quotation at the head of this review). Ewens replaced his 1969 book with *Mathematical Population Genetics* (Ewens, 1979) but did not change his view of the Fundamental Theorem, and did not mention Price. He wrote:

We make a final remark on the Fundamental Theorem, taken to be the statement that the rate of increase of mean fitness is equal to the additive genetic variance in fitness. Over the years many purported general "proofs" of this theorem have been given, some claiming the status of an authorized version, many mutually contradictory. In the previous section we have shown that for continuous-time models the theorem is exactly true only in certain special cases. For the discrete-time models we have so far considered the increase in mean fitness is not generally identical to the additive genetic variance. We show in the next section that for discrete-time models involving two loci the mean fitness can decrease. The value of such "proofs" is thus somewhat in doubt.

Happily, ten years later Ewens (1989) was to be the catalyst to the acceptance of Price's 'authorized version'.

Other books published between 1972 and 1989 which mentioned the Fundamental Theorem and might have noted Price's interpretation, but did not, include Jameson (1977), Nagylaki (1977), Spiess (1977), Roughgarden (1979), Hartl (1980), Mayo (1983), Sober (1984), and Hofbauer & Sigmund (1988). Charlesworth (1980), however, did at least refer to Price (1972), amongst others, for 'Other interpretations of the Malthusian parameter approach to age-structured models'. Bulmer's (1980) *The Mathematical Theory of Quantitative Genetics* does not mention the Fundamental Theorem explicitly, but derives the approximate expression for the total increase in mean fitness.

Of the above books, Roughgarden's *Theory of Population Genetics and Evolutionary Ecology* (1979) may serve as an example of an influential text from which students will continue to learn a view of history which should be discarded. Not only does it not refer to Price (1972), but even more remarkably it does not even refer to *The Genetical Theory of Natural Selection* itself. Instead, it states that 'The first general connection between natural selection and $\bar{w}$ was established by Sewall Wright', and later that 'Another

general theorem about natural selection is Fisher's "fundamental theorem of natural selection"'. This is held to be the continuous-time version of the growth-rate theorem mentioned in Section I. Finally, with weak selection 'we can extend Fisher's fundamental theorem of natural selection to random mating diploid populations'.

The notable exception to these strictures is Falconer (1981) who wrote 'A proof of the theorem and an explanation of why it has caused so much difficulty is given by Price (1972)' and then proceeded to use standard selection-differential mathematics to derive the result that the change in mean fitness in one generation is equal to the genic variance, apparently exactly. Since the result is certainly not exact even with only two alleles at a locus and random mating (except in the special case of no dominance) an explanation is required, and it turns out that the change in mean fitness involved in the selection mathematics is precisely the partial change envisaged by Price. The reason for this is best seen from Falconer's later account (1985): the change in the mean fitness is computed from the regression of fitness on gene frequency, but the dependence of this regression itself on the gene frequency is ignored. Falconer has evidently provided what Price had in mind when he wrote:

(It may be noted that if our aim were merely to derive the theorem rather than to explain how Fisher derived it, the derivation can be accomplished far more simply if we work entirely with regression coefficients and covariances without using Fisher's special 'average excess' and 'average effect' variables.)

Professor Falconer tells me (December 1993) that he now thinks his treatment is probably the same as one he heard from I. M. Lerner in about 1948.

In a recent long commentary to a new edition of Haldane's *The Causes of Evolution* (1990), E. G. Leigh, Jr mentions both Price (1972) and Ewens (1989) but still computes the change in mean fitness without recognizing that it is not only the gene frequency which, in his formulation, changes from one generation to the next. Like Falconer, he thus appears to obtain an exact expression for the total change in mean fitness which is in fact only the partial change as obtained by Ewens.

## XII. CONCLUSION

Fisher's Fundamental Theorem of Natural Selection is important for three reasons. First is the historical fact (Sections V and VI) that it led Wright to the idea of an adaptive topography in gene-frequency space which has dominated so much thinking in evolutionary biology. We have seen how this involved a maximisation principle of doubtful validity with which Fisher's name became associated in spite of his protests. In *Nature* in 1986 Felsenstein reviewed Provine's biography of Wright (Provine, 1986) and I challenged his view that it was Fisher, rather than Wright, who had espoused the idea of searching for the quantity evolution would maximize (Edwards, 1987). Later Felsenstein (1989), in reviewing another book this time in *Science*, associated both men with the idea, and we submitted a further interchange of views to *Science*, but they were never published. Part of Felsenstein's reply to my remarks, which I quote with his permission, seems admirably to sum up the state of affairs:

Edwards is no doubt right that Fisher [and Haldane] were fine mathematicians, and that Fisher did not draw from his Fundamental Theorem of Natural Selection the implication that natural selection would maximise mean population fitness. But historically the more important point is what lessons readers drew from their work....

Whatever Fisher thought of fitness maximization, I can testify that population geneticists of the 1960s thought that his Fundamental Theorem was a theorem that guaranteed that change of mean fitness, being expressed in terms of a variance, could *not be negative*. No doubt we misinterpreted his work, but the point is that this is how we interpreted it. Fisher's influence on subsequent generations of researchers was not to inspire skepticism of fitness maximisation; they had to rediscover its limitations for themselves. The counterexample found in Fisher's 1941 paper is relevant to a discussion of his intellectual system, but it happens to have been of no influence on subsequent researchers. My review invoked Fisher as the patron saint of this belief; this he was, even if he may not have been a believer himself.

Nagylaki (1991) went further: 'Indeed, it is fortunate that Fisher has apparently been misinterpreted, for the canonical interpretation has led *to a rich and illuminating literature*'.

Secondly, and of more permanent value, is the fact that the theorem gives mathematical precision to the previously vague notion 'that in species in which a higher proportion of the total variance is ascribable to genetic causes, the effective selection will be more intense than in species in which the variance is to a larger extent ascribable to environmental variations' (Section II). There is no point in criticizing Fisher for not having achieved more, for we now understand (what he had always understood) that an exact statement is only possible in respect of the partial change in mean fitness. As Price (1972) remarked, 'We may note that the 'fundamental theorem' is very probably the most that anyone has yet been able to say correctly about evolutionary increase in fitness under *general and realistic natural conditions*. Thus the theorem is by no means a trivial, uninteresting result'.

In a very clear account which can profitably be read as a sequel to the present review, Frank & Slatkin (1992) explain the implications of the new interpretation of the Fundamental Theorem for evolutionary biology. They ask: 'What *did* Fisher really mean by the Fundamental Theorem? Is Fisher's interpretation of the Fundamental Theorem useful? and Why was Fisher misinterpreted, even though he stated on many occasions that he was not talking about the average fitness of a population?'. In answer to their second question they write:

It is a matter of taste whether a particular partition of evolutionary change is useful; all of the component parts must ultimately sum to the same total change. We believe that Fisher's partition is useful – indeed fundamental. To support this conclusion, we analyse an interesting biological problem, the evolution of clutch size, and show that Fisher's view leads to a significantly deeper understanding of the problem.

They add, in conclusion, 'What one gains from the Fundamental Theorem...is a stronger ecological sense of the relationship between natural selection and evolution'. Not everyone agrees, however: Nagylaki (1991), whilst accepting that Price and Ewens 'have argued cogently', believed that 'the biological significance and analytical usefulness of the partial change in the mean fitness remain to be demonstrated. Thus, under the Price-Ewens interpretation, Fisher's assertion is a theorem but does not seem to provide any fundamental insight into evolution under natural selection' [the quotation earlier in this Section follows at this point]. Though Frank and Slatkin thank Nagylaki, amongst others, for his comments on their paper, they do not record what they were. Ewens (1989) also recorded a 'negative assessment of the theorem as a biological statement'. Crow, whose record of thoughtful comment on the theorem now extends over forty years, is not wholly persuaded by Ewens (1989): 'We'll never

know exactly what Fisher had in mind', but 'To me, even if Fisher's fundamental theorem is inexact and incomplete, this succinct statement captures the essence of the way selection works, and encapsulates a great deal of evolutionary insight in a simple expression' (Crow, 1990).

The third reason why the theorem is important is that correctly interpreted it has a considerable potential for future developments in mathematical population genetics. To discuss these would be beyond the scope of the present review, and the reader is referred to Ewens (1992) *An optimizing principle of natural selection in evolutionary population genetics* for an entry into the recent literature.

It will probably be many years before the name of the Fundamental Theorem of Natural Selection is returned to its originator and ceases to be attached to other related formulations. The magnitude of the task can be gauged by the appearance in the very journal which carried Ewens (1989) of a paper (Findlay, 1990) which opens: 'Fisher's fundamental theorem of natural selection states that the rate of change in the mean biological fitness of a population is equal to the additive genetic variance in fitness. Since variances are always positive, this implies that mean fitness never decreases,...'. Although the author quotes Ewens (1989) – as Ewens (1990) – his treatment of the theorem completely ignores the content of Ewens's paper.

Nagylaki (1993) has tentatively suggested that the theorem should be called the Fisher–Price–Ewens theorem, but that seems likely to confuse future generations: let the theorem (and only the theorem) carry the name its originator gave it.

I hope the present review will contribute to the process of reassessment of the Fundamental Theorem started by Price and Ewens, and that Fisher's original intentions will soon find their way into the textbooks to be discussed on their own merits.

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This paper, which seems to have been entirely overlooked since its publication, includes a section *The fundamental theorem of natural selection* in which Professor Bennett gives the clearest account of Fisher's theorem prior to the work of Price (1972).