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R. A. Fisher and Evolutionary Theory

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Abstract. R. A. Fisher, apart from his fundamental contributions to statistical science, fostered many developments of theoretical evolutionary science. In commemoration of Fisher's birth centenary (1991), this paper highlights several of Fisher's interests in evolutionary processes. These include the "Fundamental Theorem of Natural Selection," studies on the phenomenon of an even sex ratio in natural populations, the "runaway process" of sexual selection and models of polygenic inheritance. Some historical discussions and perspectives on evolutionary science and the Fisher legacy are also presented.

1. INTRODUCTION

I never met Fisher but his influence on me was profound, particularly since I established important bonds and collaborations with several of his students and post docs. The year 1990, the centenary of Fisher's birth, brought forth many symposia and publications devoted to honoring his seminal contributions to evolutionary theory and statistical science. In this article, I further this objective by reviewing four problems and controversies of evolutionary theory that intrigued and engaged Fisher.

Some background material and historical perspectives on the nature of evolutionary processes are presented in Sections 2 and 3. Section 4 focuses on Fisher's basic mathematical model of heterozygote advantage as a mechanism in maintaining genetic variability. The "Fundamental Theorem of Natural Selection" is also discussed in this context. Section 5 examines the ubiquity of an even sex ratio in natural populations and Fisher's ideas on parental expenditure to account for this. The Fisher "runaway process," proposed to explain extreme dimorphisms as a concomitant of sexual selection, is considered in Section 6. A brief analysis of Fisher's classic 1918 paper that attempts the reconciliation of Darwinism and Mendelism and gives a method of calculating correlations of relatives is considered in Section 7. The concluding section reviews some personal activities and viewpoints of Fisher that have influenced evolutionary genetics research to date.

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2. BACKGROUND: COMPONENTS AND FORCES OF EVOLUTIONARY PROCESSES

Evolutionary processes and theory study temporal and spatial changes in the numbers of possible types (e.g., genotypes, species) within one or more populations, subject to genetic, ecological and cultural influences. Two general balancing forces operate on natural populations: (1) the propensity to adaptation and persistence of specific types suited to a given environment: *determinism of natural selection*; and (2) the advantage for populations of maintaining potential for variation to cope with changing environments: *vigor of polymorphism*.

The agencies and forces acting on populations of individuals include natural and sexual selection, mutation, migration, mating patterns, recombination and linkage, varying environmental conditions, founder effects, historical influences and chance perturbations. We now annotate these factors in qualitative terms.

Forms of Natural Selection ("Fitness")

Differential viability bears on how types differ in their ability to survive. Fertility selection reflects the variation in numbers of offspring produced by the different parental crosses. Segregation distortion (meiotic drive) refers to deviation from the Mendelian (equally likely donation of parental gametes) segregation.

Mutation

Mutation events, the ultimate source of genetic variability, commonly include substitution, deletion or insertion of nucleotides in DNA chains. On a larger scale, chromosomal aberrations change the arrangement of genes or duplicate blocks of genes, or translocate segments of chromosomal pieces, etc.

The rates of mutation vary among species and are sensitive to environmental and genetic conditions.

Mating Patterns and Sexual Systems

A variety of systems exist. Parthenogenesis (asexual reproduction) is pervasive in bacterial populations and in certain insect, fish, reptile and plant populations. Many amphibians (e.g., shrimp) are sequential hermaphrodites, acting as males during part of their life and females during the other part. Most plant populations are simultaneous hermaphrodites, carrying both sex organs. In a number of plant varieties, incompatibility mechanisms (analogous to separate sexes) compel outcrossing. Among social insects (e.g., wasps, bees, ants), three classes of individuals are present: fertile males, fertile females and sterile females.

Mating behaviors can exhibit a variety of forms. Sexual selection has two primary aspects: (1) how the sexes meet—the social structure in which sexual encounters occur; and (2) having met, how mating pairs are formed—the behavioral mechanism of pairing and maintaining pairs. Social encounters often take place either in groups where males and females congregate at special sites known as leks or between individual males and females in different encounter patterns. Matings are typically polygamous in lekking groups. The mechanism of pairing may depend on male competition, female choice or both. Females are not just impartial arbiters but often make their own independent judgments between the males. They may have an inherited tendency to choose a particular male phenotype. As Fisher (1915, 1930) proposes, such mating preference will be selected if females choose in favor of selectively advantageous males.

Recombination and Sex

A significant source of new variation is the phenomenon of recombination, in which separate (usually homologous) chromosomes exchange portions of DNA at reproduction (meiosis). Tied to the recombination process is the extent of ploidy. Fungi live most of their lives as haploids (single gene dose) but take excursions as diploids (two gene doses). Vertebrates are invariably diploids, so that a gene unit carries two doses of the genetic material determining its genotype. Higher ploidy abounds in plant populations but is apparently rare in the animal kingdom. Prokaryotes (organisms whose cells lack a distinct nucleus) allow recombination from time to time mediated by processes of transformation (i.e., exchange of DNA between distinct bacterial strains), transduction (i.e., transfer of DNA material between species through viral vectors) and conjugation (a process akin to sexuality).

Environmental Factors

The interactions of natural and sexual selection forces, mutation, migration and environment are complex and subtle. These include the effects of frequency and density-dependent factors, the age structure of the population, behavioral characteristics, life history strategies, ecological covariates, species abundances and historical factors. Population size, chance factors and initial conditions all play a role in the evolutionary process. In a small population, "sampling effects" or "random genetic drift" can induce statistical (uncontrolled) variability. A deleterious mutant type can be established purely by chance.

Biological Diversity

Taxonomists have recorded about 1 to 1.5 million bacterial, plant and animal species and surmise that another 10 up to 100 million species remain to be classified (see symposium on biodiversity, August 9, 1991 issue of *Science*). The number of species throughout the evolution of life is estimated from 4 to 16 billion. Simpson (1953) asserts that over 99.9% of all species that ever existed are extinct. More than 50% of all living species are of the insect genera. Counts of bird species vary from 3,000 to 10,000.

The ubiquitous variability within species of biochemical, morphological, physiological and behavioral traits is also intriguing. As observation and experimental techniques are being refined, increasing numbers of segregating genes in populations (those exhibiting at least two alternative types) are being detected. Another aspect of nonuniformity is the prodigious variety of sexual mechanisms, mating patterns, life cycles, strategies for survival and reproduction, growth characteristics and ecosystem interactions.

Concomitant to the observed diversity in living forms and life patterns, there are some universals. The basic DNA, RNA and protein components are present in "all" organisms. And although energy conversion and production are managed in a number of ways, common to all these is the generation and use of ATP (adenosine triphosphate), the main energy source used in driving all other activities.

A central problem of evolutionary theory is how to explain the vast variability observed on all levels. How much of this and what kinds can be accounted for by natural and/or sexual selection, and what is the nature of the selection forces and causal mechanisms? Non-Darwinists ascribe to evo-

lution a significant role for chance events and founder effects in the initiation and maintenance of variability. Other questions relate to assessments of rates of change in frequency patterns within and between populations and species. Another problem is to explain the trends and forms observed in the fossil data (e.g., issues of stasis versus punctuation). For further general references, see Futuyma (1979) and Wallace (1981).

3. A BRIEF HISTORY OF EVOLUTIONARY THEORY

In my view, it is convenient to divide modern evolutionary science into five periods, as depicted in Table 1.

The Period Prior to 1900

The writings of Darwin offer an enthralling experience in observation, synthesis, inference and speculation. Darwinism, the theory of natural (1859) and sexual selection (1871), is not a set of rigorous theorems. But there is no doubt of the existence of "natural selection" underlying many changes in the composition of natural population at all levels. The significance of Mendelism (segregating genes) comes to the fore only at the turn of the century (publication appeared in 1865; see Mendel 1958). Fisher (1930) identifies Mendel as "a young mathematician whose statistical interests extended to the physical and biological sciences," who modeled his laws of inheritance to be consistent with his experimental results. Biological science prior to the mid-19th century overwhelmingly focused on classifications of plants and animals by a myriad of criteria. There was little quantitative theory and even qualitative speculations in elucidating the vast observed variability in forms, taxa and species. The aim of the Linnaean classifications of plant and animal organisms and subsequent hierarchical nomenclatures was to reduce the arbitrariness and to introduce some order. Most naturalists now view these motivations as of secondary value.

TABLE 1
Five periods of modern evolutionary science

Before 1900 (Linnaeus, Lamark, Darwin, Galton, "Mendel")	CLASSICAL DARWINISM (variation of continuous traits between and within populations)
1900-1920 (K. Pearson, Bateson)	EARLY MENDELISM the population genetics of discrete traits
1915-1955 (Fisher, Haldane, Wright)	NEO-DARWINISM reconciliation of Darwinism and Mendelism
1944-1970	First major revolution of molecular genetics (Watson Crick Model, unraveling the Genetic Code)
1955-1970	Influence of molecular biology on evolutionary theory (deluge of biochemical polymorphism)
1970-	Studies of polygenic inheritance, studies of evolution of behavioral traits
1975-	Advent of paleobiology and sociobiology, second major revolution of molecular genetics (recombinant technology)

In the latter part of the 19th century, investigators were bemused by the subtleties and variations manifested in quantitative characters and, in particular, were curious about the frequency changes of continuous traits as transmitted over successive generations in human populations. Galton (a cousin of Darwin) and K. Pearson (a protegé of Galton) pioneered the fundamentals of biometry (the precursor of modern statistical science), motivated mainly by problems of evolution and eugenics. In 1889, Galton proposed that human stature is inherited and calculated the parent offspring correlation as 0.33. He also was the first to use twin studies for the purpose of assessing the heritability of polygenic traits.

Galton proposed a model of multifactorial inheritance of the following form:

$$(3.1) \qquad X_{n+1} = h\frac{X'_n + X''_n}{2} + Y_n + a\mu_n$$

where X'_n and X''_n are the parental trait values in generation n, X_{n+1} is the trait value of an offspring, Y_n is an independent environmental contribution of mean zero, μ_n is the population mean of generation n, h^2 is the heritability coefficient (the regression of an offspring on the midparental value) and a serves as a constant scale adjusting the relative influence of the population to that of parental transmission. Where X'_n and X''_n are independent normal, $N(\mu_n, \sigma_n^2)$, variables and Y_n is distributed $N(0, b^2)$, then for $a + h < 1$, X_n has a limiting normal distribution $N(0, \sigma_\infty^2)$ with $\sigma_\infty^2 = b^2/(1 - h^2/2)$. The variance σ_n^2 converges provided $h^2 < 2$.

The analysis of (3.1) led to the principle of *regression to the mean*, where children resemble their parents but regress toward the population average, the latter concept apparently in contradiction to Mendelian principles. Later, K. Pearson in a landmark publication (1904) rejected Mendelism, but all the same this work served decisively in laying

the bridge connecting biometrical population genetics to Mendelian principles.

Galton and Pearson formalized and quantified concepts such as "population," "measures of variability" and "regression structures." They emphasized the fundamental existence of various forms of variability within and between populations. In particular, the Pearson family of distribution laws was developed to fit data on populations. The recognition of variability *within* populations led to the natural inquiry about the mechanisms causing this variability.

The Period from 1900 to 1920

The year 1900 saw the formal recognition of Mendel's work. Parenthetically, that year also marked the birth of modern quantum mechanics with Planck's celebrated formula on the relation of energy and frequency of a light photon. Mendel's famous paper of 1865 is a paradigm of experiment, observation, data analysis, deduction and abstraction. The 10 years from 1900 to 1910 further witnessed a meshing of mainly genetic plant breeding and cytological examinations with the deductive-inductive mathematical statistical method and gave proof to a renovated form of Mendelian principles and simultaneously elaborated a whole panoply of evolutionary genetic concepts. The concepts "expression of a gene," "genotype," "phenotype," "dominance," "recombination," "linkage groups," "gene mapping," "mutation," "epistasis," "heterosis," "pure lines," "inbreeding" and others as causes and agencies of evolution were crystallized and clarified. These concepts arose from what was described as "a beautiful merge of statistical and mathematical reasoning" (Dunn, 1965).

A consortium of plant physiologists, geneticists and biometricians nurtured these developments. Notable contributors included the biometricians-statisticians Galton, K. Pearson, Weldon and Yule; a wide spectrum of biologists, Bateson, Castle, Morgan (and his whole school), Garrod, Weinberg and Hardy, of mathematical fame, participated in discovering the Hardy-Weinberg Law (Hardy, 1908; Weinberg, 1908) of constancy of gene frequency; among the plant physiologists, notable contributions were made by Johannsen, Nilsson-Ehle and Jennings. The primacy of this work was genetic observation and afterwards statistical or mathematical modeling and deduction. Thus, for example, the linear order of genes was inferred from statistical analyses.

The experiments from 1900 to 1920 were done largely by agriculturists and Morgan (and associates), who exploited expeditiously the advantages of the organism *Drosophila*. Johannsen, principally, and Nilsson-Ehle foreshadowed the use of mathematical and statistical analyses as developed later by Fisher and Haldane but to an extent promulgated earlier by Galton and K. Pearson for purposes of appraising the variation due to the interaction of mutation and selection and also due to response of genotype to the environment. Johannsen studied the inheritance properties of bean seed size and shape, and realized that continuous variation could be explained by discontinuous genetical variation coupled to environmental factors. He and others manipulated genes by imposing a variety of regular systems of matings and evaluated the consequences partly with the help of mathematical methods.

The Period of 1915 to 1955

Between 1915 and 1955, theoretical evolutionary genetics was dominated by R. A. Fisher, J. B. S. Haldane and Sewall Wright.

Fisher trained as a mathematician (he was a Wrangler, indicating high honors in mathematics, at Cambridge). After his degree Fisher taught school, tried farming and served in his early career as a statistical consultant for biologists. His first efforts in genetics produced a classic paper (1918) that embodied the seminal ideas of ANOVA (analysis of variance) and aspects of the design of experiments (see Section 7). [His earlier brief papers in 1911 and 1912 contained some ideas along these lines; see Bennett (1983).] He is the indisputable founder of the theory of experimental design. His efforts to understand evolutionary and genetic theory paralleled and nurtured his statistical exploits. Fisher's monograph on natural selection (1930) is still a source of stimulation and conundrums in evolutionary theory. Although Fisher wrote about 50 papers concerned with the theory of population genetics, his main responsibility over an extended period was as chief statistician at the Rothamsted Agricultural Station. The motivation of design in agricultural layouts intermeshed with his interests in genetic theory.

The condition for selection balance at a single gene locus involving two alternative alleles (gene types), called the *overdominance principle* or *heterozygote advantage*, was modeled by Fisher in 1922. This important result provides the simplest mechanism for the existence of a stable polymorphism arising solely from the balance of differential viability effects and random mating (see Section 4). This model has effectively been used to explain the gene frequency polymorphism of the sickle cell disease trait in Central African populations.

Sewall Wright, a zoologist by training, used equilibrium principles in comparing observation with

expectation in rejecting a one-gene hypothesis for the inheritance of blue eye color in humans and in a case of color inheritance in cattle. (Felix Bernstein, a noted mathematician, in 1925 employed similar ideas to reach a correct interpretation of the inheritance of the ABO blood typings.) Wright (1923) also proposed the method of path analysis, which was the precursor of general variance decomposition methods widely used in the social sciences during the past three decades under the name of "linear structural equation model."

Haldane, whose undergraduate degree was in classics at Oxford, roamed over the sciences, history and politics and wrote popular science as well. He contributed significantly to enzyme kinetics, statistical practice and to many facets of population biology. He was competent in mathematics and statistics as well as in chemistry and genetics. In a famous series of papers on "Mathematical contributions to the theory of natural selection" that appeared in the *Proceedings of the Cambridge Philosophical Society* in the 1920s, Haldane set forth a variety of simple mathematical analyses concerned with the way natural selection might be supposed to act. He worked out the theory of different forms and intensities of selection and mutation balance and its effects on frequencies of autosomal, dominant, recessive and partial sex-linked genes. His model of *mutation selection balance* (see Section 4) is still useful in the study of genetic diseases and medical genetic counseling. This gives an estimate of equilibrium values where recurrent mutation of deleterious alleles are balanced by their elimination through selection.

Galton and Watson in 1874 (see Galton, 1889) showed that the theory of stochastic branching processes could be used to study chance effects on the development of families or populations. Their studies mainly concerned the problem of extinction of surnames in a family lineage. Specifically, if a man has probabilities $p_0, p_1, p_2, \ldots$ of having $0, 1, 2, \ldots$ sons, respectively, and each son has the same probabilities for having sons of his own and so on, what is the probability of a given number of male descendants in a given generation? Branching processes were later revitalized by Fisher and Haldane to study the degree of survival of a mutant gene in populations. More recently, the Galton-Watson model and more generalized branching processes have been extensively studied mathematically (e.g., Harris, 1963; Athreya and Ney, 1972; Jagers, 1981) and in many other applied contexts.

Wright, in 1931, established that in small populations evolutionary theory should take account of the sampling effects involved in producing one generation from the previous. He called this effect "random drift." The significance of Wright's sampling force has become a focal point of a sharp controversy on the nature of the evolutionary process (the neutralist-selectionist controversy). Evolution can be considered to be a sequence of gene replacement processes, whereby in each such process one allele is replaced in a population by another allele. Classical Darwinian theory maintains that the replacing allele is superior to the replaced allele and that the mechanism directing the replacement procedure is natural selection. The essence of the neutralist theory is that a large proportion of the replacement processes has arisen purely as a result of chance phenomena acting on selectively equivalent alleles and, just by chance, the individuals carrying a new mutant allele happen to leave more offspring than the remaining individuals. Thus, the changes due to random genetic drift in small population could be nonadaptive. Parenthetically, the work of Wright on genetic models of finite size population was the prime stimulus for the boundary theory of diffusion processes (cf. Feller, 1951).

Table 2 highlights six key topics and works of evolutionary theory that keenly occupied Fisher. These are only a few of many areas in which Fisher made notable contributions. The underlying concepts of the first four will be detailed in the subsequent sections.

Fisher, a confirmed selectionist in his viewpoints, wrote two books on these subjects. *The Genetical Theory of Natural Selection* (1930), virtually biblical in style and content, contains numerous developments, insights, opinions, and obscure tantalizing sentences and challenging hypotheses. The later book on *The Theory of Inbreeding* (1949) is primarily technical.

The Period from 1960 to the Present

The main directions of recent research in evolutionary theory include at least six major areas:

1. Multilocus (Multigene) Studies. Studies of complex genetic systems integrating the interactive effects of several agents and relations among loci. For a review of n-locus selection models, for example, see Karlin and Avni (1981) and Christiansen (1989a, b). The last three decades have also witnessed a renewal of activity devoted to the elaboration of dynamic models on polygenic and quantitative characters. A strong motivation stems from interest in the heritability of behavioral, physiological and medical conditions, for example, coronary risk factors, cognitive traits and connections to cultural transmission. Recent theoretical and mathematical models of multifactorial transmission occur in many writings (consult Weir,

TABLE 2
Key studies of R. A. Fisher in evolutionary theory

Model of heterozygote advantage (Fundamental Theorem of Natural Selection)	Section 4
Models of evolution of sex ratio	Section 5
"Runaway process" of sexual selection	Section 6
Assortative mating model of polygenic inheritance (1918 paper—correlations of relatives)	Section 7
Selection-migration interactions, wave of advance (1950)	
Method of diffusion processes in genetics (1930 book)	

Elsen, Goodman and Namkoong, 1988, and references therein on quantitative inheritance).

2. Variation in Natural Populations in Space and Time. The quantification of the interaction of environmental-ecological profiles, population structure and evolutionary development has, over the last 30 years, become a subject of wide-ranging investigation both on the empirical and theoretical fronts. (For reviews, e.g., see Nagylaki, 1978b; Karlin, 1982.)

3. The Study of Stochastic Genetic Models. Many advances in the theoretical description of random genetic drift have been inferred from results and techniques of *diffusion* stochastic processes. First Fisher (1930) and Wright (1931) and later chiefly Kimura (1983), and many others, extensively applied diffusion analyses to the study of stochastic genetic models; see the books of Ewens (1979), Kimura (1983) and the recent edited volumes by Lessard (1987) and Feldman (1989).

The neutralist-selectionist controversy especially has uncovered many natural stochastic models. These include the Ewens sampling formula (1972) and its intimate connections with Poisson-Dirichlet processes. For an elegant review with several new results and perspectives, see Kingman (1980); charge state models, Watterson (1975); wandering profile models, Moran (1975) and Kingman (1976); genealogical stochastic structures, Kingman (1980), Hoppe (1984) and Tavaré (1984); coalescent and ancestral processes, Kingman (1982a, b), Watterson (1984) and Donnelly (1991).

4. The Formulation of Mixed Genetic, Demographic and Ecological Systems. A triumvirate pioneered the subject starting in the early 1920s; see Lotka (1925), Volterra (1931) and Kositizin (1937). Recently the interaction of demographic, ecological and genetic systems has become a major focus of evolutionary studies (for a review, see Ginzburg, 1983; Demetrius, 1992).

5. Studies in the Population Genetics of Behavioral Traits. Attempts have been made to quantify the evolution of behavioral traits in the areas of group selection, kin selection and the evolution of altruism. Theoretical and qualitative modeling along these lines have been done by Wynne-Edwards (1962) and Hamilton (1964), and mathematical formulations by Boorman and Levitt (1980), Uyenoyama and Feldman (1980), Karlin and Matessi (1983) and Matessi and Karlin (1986). Observation, speculation and theorizing about behavioral patterns and organizational structure by ethologists and naturalists such as Tinbergen, Lorenz, E. O. Wilson and G. C. Williams have been of great help in understanding the structure of certain animal and insect societies. In this literature, the genetic basis of population control, mimicry, signaling and alarm calls in prey-predator situations, communication systems and hierarchical status in groups are discussed in terms of strategy analysis, and the role of kin selection is underscored.

6. The Evolutionary Dynamics of RNA Molecules, Viruses, Introns, Enzymes, etc. For a recent review, see Ratner (1990) and references therein.

4. THE FUNDAMENTAL THEOREM OF NATURAL SELECTION

We review first Fisher's (1922) important model of heterozygote advantage. Consider a large population comprised of two possible gene (allele) types A and a undergoing random mating and subject to differential viability selection. Specifically, the genotypes AA, Aa and aa survive to reproduce in the ratio $\sigma_1 : \sigma_2 : \sigma_3$, respectively. If the frequency of $A(a)$ in the present generation is $p(q = 1 - p)$, then random union of genes (equivalent to random mating) produces the genotype frequencies p^2, $2pq$, q^2 for AA, Aa, aa, respectively.

The relative frequencies of the three productive genotypes are then $\sigma_1 p^2, \sigma_2 2pq, \sigma_3 q^2$. Following Mendelian segregation, the A-gene frequency of the next generation is

$$(4.1)\quad p' = \frac{\sigma_1 p^2 + \sigma_2 pq}{\sigma_1 p^2 + 2\sigma_2 pq + \sigma_3 q^2} = f(p).$$

For $\sigma_2 > \sigma_1, \sigma_3$ the population evolves (that is, the iterates $f_n(p) = f_{n-1}(f(p))$ converge) to the intermediate stable gene frequency $p^* = (\sigma_2 - \sigma_3)/(2\sigma_2 - \sigma_1 - \sigma_3)$. (For all other fitness relationships, the population settles to a fixation state where either $p^* = 0$ or $p^* = 1$.) The circumstance $\sigma_2 >$

σ_1, σ_3 is called *heterozygote advantage* (the heterozygote survives the best).

The foregoing analysis indicated the first formal mechanism allowing for natural selection effects leading to stable polymorphism. It was later verified empirically that the sickle cell anemia disease could reach high frequencies because of selective advantage of the heterozygote in malaria regions where the disease afflicting the heterozygotes was observed to be less frequent. This hypothesis was proved to be correct in Africa for sickle cell anemia by Allison (1954a, b) and is believed to hold also for other genetic diseases including thalessemia and G6PD deficiency in Mediterranean populations. In sickle cell (A = normal form and S, C, E mutant forms), the frequency of S reaches $q^* = 16\%$ in central Africa. Sickle cell anemia was dubbed by L. Pauling "the first molecular disease."

In 1927 Haldane analyzed a simple model of mutation-selection balance:

genotypes	AA	Aa	aa
relative viabilities	1	$1 - hs$	$1 - s$
	($0 < s < 1$, h = degree of dominance, $0 \le h \le 1$),		

obviously favoring the AA genotype; in this representation, a completely recessive disease has $h = 0$. Recurrent mutation $A \to a$ is assumed at the rate μ per individual per generation. For μ very small it can be proved easily with a recursion paraphrasing (4.1) that a stable equilibrium a-gene frequency is approximately $\sqrt{\mu/s}$ for $h = 0$. This model was fitted to the cystic fibrosis disorder, yielding $q^* \approx 1/2000$. The actual gene underlying cystic fibrosis was mapped only in the last two years to human chromosome 7.

The importance of the one-locus multiallelic selection balance model was reorganized and worked on by Fisher and his students. Normal eukaryotic genes are invariably multiallelic (multitype) involving exons, introns and *cis*-regulatory elements generally inherited as a unit. The discovery of elaborate gene machinery including mRNA transcription of flanking regions and intervening segments with subsequent processing of deletions and splicings adds further to the multiplicity and complexity of the allelic spectrum. Moreover, multiple alleles have been documented for many morphological, physiological, serological and electrophoretic markers. These include genes responsible for color and shape patterns (e.g., banding for snail, color for butterflies), a host of red and white blood typings (e.g., ABO, Duffy, HLA), incompatibility and sex determinants (e.g., *Hymenoptera*-ants, bees) and segregation distorter genes.

Consider a population characterized by r alleles $A_1, A_2, \ldots, A_r$ at an autosomal locus with associated genotypes A_iA_j. Under the effects of viability selection, random mating and Mendelian segregation, the parameters of the model are as follows. The viability fitness matrix for females is $F = \|f_{ij}\|_1^r$ and for males $M = \|m_{ij}\|_1^r$, respectively, where the quantity $f_{ij}(m_{ij})$ is interpreted as the relative number of A_iA_j female (male) offspring that survive to contribute to the next generation. Let the frequency of genotype A_iA_j in the female population be denoted by $2p_{ij}$ when $i \neq j$, and p_{ii} for $i = j$. Accordingly, the frequency of allele A_i in this population is $p_i = \sum_{j=1}^r p_{ij}$. The corresponding frequencies for the male population are denoted by $2q_{ij}$, q_{ii} and q_i.

Under viability selection the results from random mating are equivalent to random union of gametes (e.g., see Kempthorne, 1957; Karlin, 1978), and therefore the frequency of A_iA_j offspring is $p_iq_j + q_ip_j$. Taking account of viability selection and Mendelian segregation for a 1:1 sex ratio, the genotypic frequencies over two successive generations obey the recursion relations

$$q'_{ij} = \frac{m_{ij}(p_iq_j + q_ip_j)}{2w}, \quad p'_{ij} = \frac{f_{ij}(p_iq_j + q_ip_j)}{2v},$$

where $w = w(\mathbf{p}, \mathbf{q}) = \sum_{i,j} m_{ij}p_iq_j$ and $v = \sum_{i,j} f_{ij}p_iq_j$.

It follows that the allele frequencies p'_i and q'_i of the next generation are calculated from the transformation equations [in vector notation, writing $a \circ b = (a_1b_1, a_2b_2, \ldots, a_rb_r)$ and $\langle \mathbf{a}, \mathbf{b} \rangle = \sum_{i=1}^r a_ib_i$],

$$\begin{aligned} \mathbf{p}' &= \frac{1}{2}\frac{\mathbf{p}\circ F\mathbf{q} + \mathbf{q}\circ F\mathbf{p}}{\langle \mathbf{p}, F\mathbf{q} \rangle}, \\ \mathbf{q}' &= \frac{1}{2}\frac{\mathbf{q}\circ M\mathbf{p} + \mathbf{p}\circ M\mathbf{q}}{\langle \mathbf{p}, M\mathbf{q} \rangle}. \end{aligned} \tag{4.2}$$

The designation $\mathbf{p}\circ F$ stands for the matrix product $\mathbf{D}_\mathbf{p}F$ where $\mathbf{D}_\mathbf{p}$ is the diagonal matrix having the components of $\mathbf{p}$ down the main diagonal.

In the case $M = F$ (such that selection operates on the male and female zygotes in the same manner), then $\mathbf{p}' = \mathbf{q}'$, and in all subsequent generations the transformation T can be reduced to the single recursion (ratio of quadratics)

$$\mathbf{p}' = \frac{\mathbf{p}\circ M\mathbf{p}}{\langle \mathbf{p}, M\mathbf{p} \rangle} = S\mathbf{p}, \tag{4.3}$$

where the sexes need not be distinguished. For the case of $r = 2$ alleles, the transformation (4.3) is equivalent to Fisher's equation (4.1).

The analysis of the transformation S, its convergence and equilibrium properties, has received much attention (e.g., see the books of Crow and Kimura, 1970, and Ewens, 1979). The *mean fitness function*,

$$(4.4) \qquad w(\mathbf{p}) = \sum_{i,j=1}^{r} m_{ij} p_i p_j = \langle M\mathbf{p}, \mathbf{p}\rangle,$$

provides a strict Lyapounov function for the mapping $\mathbf{S}$, such that

$$(4.5) \qquad w(S\mathbf{p}) \geq w(\mathbf{p}) \text{ with equality if and only if } \mathbf{p}' = S\mathbf{p} = \mathbf{p}.$$

This remarkable property is sometimes referred to as the *discrete form of the fundamental theorem of natural selection* (Crow and Kimura, 1970, Chapter 5; Ewens, 1979, Chapter 2). Inequality (4.5) reduces to

$$(4.6) \qquad \sum_{i,j} m_{ij} p_i p_j w_i w_j \geq \left[w(\mathbf{p})\right]^3,$$

where $w_i = \sum_{j=1}^{r} m_{ij} p_j$, $i = 1, 2, \ldots, r$.

An elegant proof appears in Kingman (1961a, b). (Sir John Kingman, as an undergraduate, was a student of A. R. G. Owens, who was an assistant of Fisher.) A wider perspective derives inequality (4.6) as a special case of the generalized moment inequality

$$(4.7) \qquad \left(\frac{\langle C\mathbf{x}, \mathbf{x}\rangle}{\langle \mathbf{x}, \mathbf{x}\rangle}\right)^k \leq \frac{\langle C^k\mathbf{x}, \mathbf{x}\rangle}{\langle \mathbf{x}, \mathbf{x}\rangle},$$

where $C = \|c_{ij}\|_1^r$ is a symmetric matrix of positive elements, $\mathbf{x} = (x_1, x_2, \ldots, x_r)$ a positive vector and k a positive integer.

Equation (4.6) can be deduced from (4.7) with $k = 3$. Indeed, applying (4.7) to the matrix $C = D_{\sqrt{\mathbf{p}}} M D_{\sqrt{\mathbf{p}}}$, where $\sqrt{\mathbf{p}} = (\sqrt{p_1}, \sqrt{p_2}, \ldots, \sqrt{p_r})$, the left-hand side of (4.6) is (since $\langle \sqrt{\mathbf{p}}, \sqrt{\mathbf{p}}\rangle = \sum p_i = 1$)

$$\begin{aligned}\langle M(\mathbf{p} \circ M\mathbf{p}), \mathbf{p} \circ M\mathbf{p}\rangle &= \langle C^3\sqrt{\mathbf{p}}, \sqrt{\mathbf{p}}\rangle \\ &= \langle C^3\sqrt{\mathbf{p}}, \sqrt{\mathbf{p}}\rangle / \langle \sqrt{\mathbf{p}}, \sqrt{\mathbf{p}}\rangle \\ &\geq \left(\langle C\sqrt{\mathbf{p}}, \sqrt{\mathbf{p}}\rangle\right)^3 = \langle M\mathbf{p}, \mathbf{p}\rangle^3,\end{aligned}$$

the last inequality being a consequence of (4.7). The cases of equality can also be analyzed.

A recurrent theme in Fisher's 1930 book and other writings centers on what he called "The Fundamental Theorem of Natural Selection" stated in the form "*The rate of increase in fitness of any organism at any time is equal to its genetic variance at that time*," and often set in the equation

$$(4.8) \qquad \frac{d\overline{m}}{dt} = Vg(\overline{m}),$$

where $\overline{m}$ is fitness as a Malthusian population growth parameter and $Vg(\overline{m})$ refers to the additive genetic variance. Proofs, reformulations, interpretations and exegeses of this principle abound. Crow (1990b) writes, "No doubt this is an important idea but exactly what does it mean?" Edwards (1990), in his tribute to Fisher, offers some recent perspectives.

The mean fitness function for the multilocus or two-sex models involving differential selection effects unlike (4.5) is generally not increasing over successive generations (e.g., Moran, 1964; Karlin, 1975; Ewens, 1989). The formulation and interpretation of the Fundamental Theorem of Natural Selection remains cryptic. At best, Fisher's description on change of mean fitness is a within population property and bears no consequences on understanding macroevolutionary change such as extinction and speciation.

Motivated by Fisher's simple (one-locus two allele) overdominance model, we may inquire concerning an appropriate notion of overdominance for a one-locus *multiple* allele viability model and in the context of several loci. We may state tautologically under viability selection that overdominance occurs if a stable polymorphism exists. Unfortunately, this concept is inadequate in several respects. For example, for an overdominant viability matrix M, suppose M is modified to the new viability matrix $\hat{M} = M - D$, where D is a diagonal matrix $D = \text{diag}(d_1, d_2, \ldots, d_r)$ and $m_{ii} \geq d_i \geq 0$. After this perturbation, the viability array of $\hat{M}$ retains the identical heterozygote viability values as M but the homozygote viability values may be diminished. A natural inquiry: Is $\hat{M}$ overdominant? The answer can be in the negative. However, there is a stronger notion of overdominance that preserves natural properties of stable polymorphic arrays. Qualitatively, we say that a viability matrix W is *totally overdominant* if any subcollection of alleles can maintain a stable equilibrium restricted to these alleles that is unstable with the introduction of any new allele. This notion applies to various natural classes of viability matrices based on allelic activity values, selection reflecting partial or complete dominance relations and selection induced by patterns of multilocus associations (Karlin, 1981). Moreover, if $\mathbf{W}$ is *totally overdominant*, then $\mathbf{W} - \mathbf{D}$ ($\mathbf{D}$ positive diagonal) is also *totally overdominant*. The concept can also be used in terms of models of ecological resource utilization

to establish species equilibria for a natural class of competition systems (Karlin, 1990).

Another interesting question concerns characteristics of the population frequency array at a stable equilibrium. Let u_{ij} be the population frequency of the *ordered* A_iA_j genotype such that allele A_i is contributed from the maternal side and A_j is donated from the paternal side. We assume parental symmetry so that $u_{ij} = u_{ji}$. The A_i allele frequency in the population is

$$u_i = \sum_j \left(\frac{u_{ij} + u_{ji}}{2} \right).$$

When does the population frequency array $\| u_{ij} \|$ *entail heterozygote excess (or deficiency)*? For two alleles we would compare u_{12} with u_1u_2. Observe that $u_1u_2 - u_{12} = (u_{11} + u_{12})(u_{21} + u_{22}) - u_{12}(u_{11} + u_{12} + u_{21} + u_{22}) = u_{11}u_{22} - u_{12}^2$. A multiallelic generalization natural to evolutionary models of viability and familial selection is as follows.

A population polymorphic state $U = \| u_{ij} \|$ with all $u_{ij} > 0$ is said to show *heterozygote excess* if all its eigenvalues distinct from the Frobenius eigenvalue (the largest positive eigenvalue of U) are *negative* (equivalently, all the eigenvalues of $V = \| u_{ij}/u_i \|$ distinct from 1 are negative) and *heterozygote deficiency* if V has only positive eigenvalues.

For an *overdominant matrix* $W = \| w_{ij} \|$, we might expect at a polymorphic stable equilibrium an increased average heterozygote fitness in the adult population (i.e., after selection) compared to the whole population. Indeed, we have

$$\frac{\sum_{i \neq j} w_{ij} u_i^* u_j^*}{\sum_{i \neq j} u_i^* u_j^*} > \sum_{i,j} w_{ij} u_i^* u_j^*,$$

where u_j^* is a polymorphic equilibrium, and this is an easy consequence of the mean fitness inequality (4.5).

5. SEX RATIO THEORY

The evolution of the sex ratio has been considered from many perspectives. Although anomalous brood sex ratios, especially in certain insect populations, have been documented, the predominance of the 1:1 sex ratio in mammalian and avian populations is unambiguous. Why? The propensity toward an equal representation of males and females was understood by Fisher in terms of the reproductive advantage for the rarer sex. Fisher (1930) proposed that such a ratio should be obtained in the long run at least in random mating populations, since an individual increases its contribution to succeeding generations by "investing" more of its reproductive potential in the sex that is less numerous at the time of investment. In this vein, a number of behavioral models based on the precept of parental expenditure that can result in an even-sex ratio in random mating populations have been formalized (Bodmer and Edwards, 1960).

Fisher's thesis, in simple parlance, is that the sex in the minority is in high demand as a sexual mate. Recent experimental tests on silverside fish claim to have corroborated Fisher's theory. Sex in silverside fish is determined in part at birth by the temperature of the water. It is shown that sex ratio of these fish held constant at 1:1 independently of the conditions in the laboratory (Conover and Van Voorhees, 1990).

The variety and complexity of sex-determining systems and controls are under intense study in numerous articles and books (e.g., Bell, 1982; Charnov, 1982; Bull, 1983; Karlin and Lessard, 1986). Sex determination can be classified into seven modes: (1) one-locus multiallele autosomal or sex linked; (2) multigene (and polygenic) with modifier gene effects; (3) chromosomal heteromorphism, including distinguished XY-male (mammals), ZZ-male (birds) or XO-male (insects); (4) hermaphroditism (simultaneous-plants or sequential-shrimp); (5) mixed parthenogenesis (e.g., haplodiploid systems, fertilized eggs-females, unfertilized-males) as occurs with ants, bees, wasps and mites; (6) environmental sex determination (e.g., influenced by cytoplasmic milieu or endogenous conditions at birth; operational in turtles, alligators); (7) extrachromosomal factors (e.g., viral particles, contagion and conditions fostering meiotic drive). In broad terms, there are distinguished genotypic and environmental determinants subject to zygotic, parental or population controls.

Several kinds of questions arise in consideration of sex ratio evolution. (1) Under what conditions is a 1:1 sex ratio advantageous? (2) What is an optimal sex order and time of sex change for sequential hermaphrodites? (3) Why is simultaneous hermaphroditism so common in higher plant populations? (4) What is the domain of dioecy (separate sexes) versus hermaphroditism? (5) What are advantages and disadvantages of environmental versus genetic sex determination systems?

Fisher proposed that the aggregate genetic contribution to the next generation of all females is equal to that of all males, implying that members of the rarer sex individually contribute relatively more than members of the more abundant sex. Many authors discuss aspects of parental strategies, short- versus long-term fitness, individual versus populational emoluments and influences of patchy versus fine environmental conditions directed toward sex ratio controls. Their verbal

arguments contend that many of these opposing considerations are best reconciled by a 1:1 sex ratio. In most of these treatments, the actual sex determination mechanisms (i.e., the underlying multiallelic or multiloci factors) are not explicitly considered.

An alternative point of view holds that sex ratios arise as an evolutionary concomitant of the sex determination system—simply the consequence of the cytological machinery. For example, the XY/XX system and the formal Mendelian rules help produce and maintain a 1:1 sex ratio. This does not answer the question: How did it evolve and for what reasons? Moreover, sex-dependent fitness components, variants of parthenogenesis, forms of hermaphroditism and sex conversion may all affect the sex ratio.

A 1:1 sex ratio seems to predominate in most animal species in the early stages of development, although a smaller number of males would seem a priori more advantageous. Sex chromosomes overwhelmingly induce a 1:1 sex ratio at conception (but there are counterexamples). Sex determination under two blocks of genes often shows a 1:1 sex ratio even in haplodiploid organisms. Also, selection of X-linked genes that determine or affect the sex of offspring can produce a stable 1:1 sex ratio.

There are two main approaches to understanding the causes and effects of sex ratio. One emphasizes the optimization and adaptive functions of sex allocation, the other the consequences of the genetic sex-determination machinery.

An example of the first approach predicting a 1:1 sex ratio attributed to Fisher (Eshel, 1975) goes as follows. Consider a three-generation population (I, grandparents; II, parents; III, children) in which generation II consists of n_1 males and n_2 females, which produce an aggregate of N offspring in generation III. Then the average number of children for a male of generation II is N/n_1 and the average number of children for a female of generation II is N/n_2. Say a grandparent of generation I has a total of m offspring consisting of x males and $m - x$ females. In this situation, the expected number of descendants in generation III for a grandparent of generation I is

$$T = x(N/n_1) + (m - x)(N/n_2)$$
$$= mN/n_2 + (1/n_1 - 1/n_2)Nx.$$

T is an increasing function of x when $n_2 > n_1$, but a decreasing function of x when $n_2 < n_1$. Therefore the expected number of children of a grandparent in generation I increases if he or she produces more offspring of the underrepresented sex. If each grandparent makes an equal genetic contribution to each of its progeny, the expected sex ratio is 1:1. When males "cost" ϕ compared to 1 for females (ϕ is analogous to a viability differential factor for males as against females) and the total "parental expenditure" is constant, the expected male to female sex ratio at conception is $1:\phi$ such that parental expenditure is equalized between the sexes for disparate costs in rearing males and females. The sex ratio at the end of parental care remains 1:1.

Shaw and Mohler (1953) gave the following analysis of sex ratio evolution. They consider a dioecious random mating population with normal brood sex ratio M. If a deviant female adopts a sex ratio m, the relative number of her genes transferred to the third generation through her male offspring is m/M compared to 1 for a typical female and the number transferred through her female offspring is $(1 - m)/(1 - M)$ compared to 1; the total number is then $m/M + (1 - m)/(1 - M)$ compared to 2 for a typical female. Elementary analysis of this quantity shows that for $M \neq 1/2$ there exists a value m closer to $1/2$ that gives a greater contribution of genes to the subsequent generations, and that for $M = 1/2$ there is no such m.

Random mating and Mendelian segregation seem to be a priori conditions for 1:1 population sex ratio outcomes. A numerical parity between the sexes is then believed to be optimal, males and females having the same individual "reproductive value" (Fisher, 1930) on the basis that each sex provides half the (autosomal) genetic material to the future gene pool. On the other hand, sex-linked meiotic drive effects and population structures that impose more reproductive constraints on sibs of one sex or the other are likely to bias the sex ratio outcome. The Fisher sex ratio model (1930) can be summarized succinctly as follows. Let R be the maternal resource to be divided among sons and daughters. He proposed the law

$$\frac{\text{number of sons}}{\text{number of daughters}} = \frac{\text{cost of one daughter in terms of } R}{\text{cost of one son}}. \tag{5.1}$$

For the remainder of this section, we discuss more formally a general multiallelic model of sex determinations. Examples of sex controls based on multiple alleles or loci include the wasp *Habrobracon* (9 to 11 alleles), some poecilid fishes (polygenic), platyfish (3 to 4 alleles), toad (*Bufo bufo*) (with both male and female heterogamety), the mosquito

Aedes aegypti (involving multiple alleles and modifiers) and the wood lemming (a rodent) (3 to 4 alleles).

Consider a bisexual population with r possible alleles $A_1, A_2, \ldots, A_r$ at an autosomal locus primarily responsible for sex determination. We denote the frequency of genotype A_iA_j in the female population by $2p_{ij}$ when $i \neq j$ and by p_{ii} when $i = j$. The frequency of allele A_i is $p_i = \sum_{j=1}^{r} p_{ij}$. The quantities $2q_{ij}$, q_{ii} and q_i are defined analogously with respect to the male population. We assume discrete generations, random mating, Mendelian segregation and equal fertility for all mating types. Let m_{ij} be the probability for an A_iA_j offspring to become a male and $1 - m_{ij}$ that of being a female. Clearly, $0 \leq m_{ij} = m_{ji} \leq 1$. We refer to $M = \| m_{ij} \|_{i,j=1}^{r}$ as the *sex-determination coefficient matrix*. The case $0 < m_{ij} < 1$ may reflect the effects of modifier genes coupled to prenatal or neonatal interactions. When m_{ij} is 1 or 0 only, the sex phenotype is determined such that the collection of all genotypes A_iA_j partition into two groups, $\mathcal{G}_M$ and $\mathcal{G}_F$, where every individual of type $\mathcal{G}_M$ and $\mathcal{G}_F$ is unambiguously male and female, respectively. We refer to this situation as *dichotomous* (exact) *genotypic sex determination*.

For the general model, we find that the genotype frequencies over two successive generations obey the recursion relations

$$q'_{ij} = \frac{m_{ij}(p_iq_j + p_jq_i)}{2w},$$
$$p'_{ij} = \frac{(1 - m_{ij})(p_iq_j + p_jq_i)}{2(1 - w)}, \quad i, j = 1, \ldots, r, \tag{5.2}$$

where $w = \sum_{i,j=1}^{r} m_{ij}p_iq_j$ is the proportion of males, the *sex ratio*, in the total population for the given allelic frequency state.

The allele frequency changes are given by the equations

$$q'_i = \frac{p_i \sum_j m_{ij}q_j + q_i \sum_j m_{ij}p_j}{2w},$$
$$p' = \frac{p_i \sum_j (1 - m_{ij})q_j + q_i \sum_j (1 - m_{ij})p_j}{2(1 - w)} \tag{5.3}$$

and we recognize this system as a special case of the two-sex viability model, (4.2) of Section 4.

The analysis of the transformation equations (5.3) is done in Karlin and Lessard (1986, Chapters 2 and 3). There emerge two kinds of equilibria: *genotypic* and *phenotypic*. A genotypic equilibrium is characterized by identical allele frequencies for the male and female populations; it tends to show a biased (non 1:1) population sex ratio and is vulnerable to allelic mutational substitutions that are generally in the direction of reducing the bias. By contrast, a phenotypic equilibrium persistently shows a 1:1 population sex ratio, but this ratio can be realized by many genotypic frequency configurations. Phenotypic equilibria are structurally stable; that is, they cannot be altered by mutational events, although the underlying genotypic frequencies may change.

Optimality properties of phenotypic equilibria can be established. In the basic sex determination model of r alleles, the optimality property for an even sex-ratio evolution is understood to mean that, with the introduction of a new allele (from r to $r + 1$ alleles), all possible equilibrium states that are stable for the extended model cannot attain a sex ratio farther from 1:1 than the existing ratio in the r-allele subsystem. This expresses an evolutionary tendency toward an even sex ratio. A sex ratio that is evolutionarily "optimal" has the property that under modifications by successive mutant genes any deviant sex ratio would normally evolve to a sex ratio closer to this optimum. The 1:1 population sex ratio is optimal in this sense. This finding applies to sex determination under zygotic or parental controls in diploid and haplodiploid populations.

When the genotype-phenotype classes of sex determination at one locus are not absolute; that is, for $0 < m_{ij} < 1$, a stable non-1:1 sex ratio is possible according to Theorem 3.3 of Karlin and Lessard (1986). This may be the case if a probabilistic mechanism is imposed by virtue of endogenous or exogenous genetic and environmental covariates. It can be proved that if exact genotypic sex determination ($m_{ij} = 0$ or 1 for all i, j) delimits the sex dimorphism of the two phenotype classes in such a way that $\mathcal{G}_M$ consists of all genotypes with $m_{ij} = 1$ and $\mathcal{G}_F$ consists of all genotypes with $m_{ij} = 0$, then *only a 1:1 population sex ratio can be stable.*

The study of multifactorial sex determination is relevant in at least two contexts. First, the sex phenotype may be influenced by many loci (e.g., mediated through some developmental or physiological process), as is probable with various fish, amphibian, reptile and invertebrate species. Second, environmental sex determination (e.g., where sex depends on nesting temperature) probably reflects a complex situation of gene-environment interactions.

The main conclusion that emerges from our studies of multifactorial sex determination is that a non-1:1 population sex ratio is expected when environmental pressures affect the sexes

asymmetrically, or when paternal or maternal genetic or phenotypic contributions are unequal.

Non-even sex ratios are also promoted by multilocus determinants of sex expression under loose linkage. The prevalence of non-even sex ratios among invertebrates leads to the hypothesis that the sex factors in many fish, amphibian, reptile and invertebrate species are not confined to a single gene but are distributed over the genome.

For recent multilocus sex ratio evolution studies, see Feldman, Christiansen and Otto (1991), Liberman et al. (1990), and Nordborg (1991).

6. SEXUAL SELECTION AND FISHER'S "RUNAWAY PROCESS"

Darwin (1871) in studying the sometimes extreme dimorphism (e.g., distinctive visual and acoustical displays—in birds, frogs, fish) of secondary sexual characters (generally expressed in adults during mating season) considered the possible effects of sexual selection caused either by competition for mates between individuals of one sex, or by female choice preference. For very recent field studies in this respect, see Andersson (1990) and Ryan (1990). It is observed, particularly in polygamous species, that great variation in mating success within the chosen sex (usually males) can arise, with a strong consequent influence on the genetic evolution of the population. Even for monogamous systems, Darwin suggested that there may still be an advantage in being a preferred male, since this would lead to mating earlier in the breeding season when nutritional conditions are superior. O'Donald (1980, Chapter 7) has demonstrated this phenomenon in operation in the mainly monogamous Arctic skua bird.

Two primary forms of sexual selection are *female choice* and *male competition*. Female choice is effected often through visits of the female to lekking groups (gathering sites for males and females during mating seasons) or in a more individual behavioral encounter context (e.g., see O'Donald, 1980). Discussions on the persistence of extreme traits weigh advantages conferred by mating success versus viability loss. Another view emphasizes the extreme trait as an isolating mechanism such that the display serves as an unambiguous cue preventing individuals from mating wrongly. For example, the Tungara frog has conspicuous calls and males evolve to a pre-existing bias in calls; although these male displays may attract appropriate females, they can also bring dangerous predators. Some students of sexual selection postulate that *good genes* correlate with unusual displays. Hamilton and Zuk (1982) hypothesize that bright colorations are associated with resistance to parasites (diseased males tend to be more pale), which is recognized in female choice.

The problem of how extreme selectivity in mating can come into being, and how preference and character might evolve together, is the context of Fisher's succinct proposals (1930, 1958). He writes "whenever appreciable differences exist in a species, which are in fact correlated with selective advantage, there will be a tendency to select also those individuals of the opposite sex which most clearly discriminate the difference to be observed, and which most decidedly prefer the advantageous type." Modification of the male character will then proceed "under two selective influences: (i) an initial advantage not due to sexual preference, which advantage may be quite inconsiderable in magnitude, and (ii) an additional advantage conferred by female preference." Male character and female sexual preference "must thus advance together, and so long as the process is unchecked by severe counterselection, will advance with ever-increasing speed." The idea is that there will be a "runaway," which will continue beyond the point where the initial advantage has been passed, and indeed will go on until the character's development is so extreme that, in terms of selective forces other than sexual selection, it is now disadvantageous and this counterselection brings the process to a halt. In polygamous species, this is known as "Fisher's Runaway Process."

Many have tried to quantify Fisher's proposal for how character and preference may evolve jointly (e.g., O'Donald, 1962, 1967, 1980, 1990; Lande, 1981; Kirkpatrik, 1982, 1987; Tomlinson and O'Donald, 1989; Karlin and Raper, 1990). We briefly review the model of Karlin and Raper (1990) (cf. Lande, 1981) on the *runaway process* in the context of quantitative characters with its qualitative predictions.

We suppose for simplicity that the character may be measured by a single scalar value. The preferences of each female will be expressed on the same scale as the male character itself. Both sexes carry genetic information for both traits: the character and the preference. Let $\mathbf{x}$ denote the phenotypic trait in males of two components with x_1 giving the character value and x_2 the (unexpressed) preference value. Let $\mathbf{y}$ denote a typical female trait vector. We shall consider a model of a large population reproducing in discrete generations. Assuming there are no differences between the sexes in the mode of inheritance and the action of the perturbing forces (mutation, environment, etc.), the distributions $p(\mathbf{x})$ of $\mathbf{x}$ and $p(\mathbf{y})$ of $\mathbf{y}$ at the zygote stage will be the same in any particular generation.

Let $s(\mathbf{x})$ and $t(\mathbf{y})$ be the relative viabilities of males and females with phenotype values $\mathbf{x}$ and $\mathbf{y}$, respectively. Let $\psi(\mathbf{x},\mathbf{y})$ be the relative conditional probability for a male of phenotype $\mathbf{x}$ and a female of phenotype $\mathbf{y}$ to mate; encounters occur in proportion to their frequencies in the adult population. Assume that males mate polygamously, but females mate once and with equal fertility. Then the joint distribution of mating pairs is given by

$$\tilde{p}(\mathbf{x},\mathbf{y}) = \frac{p(\mathbf{x})s(\mathbf{x})\psi(\mathbf{x},\mathbf{y})p(\mathbf{y})}{\int p(\mathbf{u})s(\mathbf{u})\psi(\mathbf{u},\mathbf{y})d\mathbf{u}}.$$

We stipulate that transmission is given by the midparental value plus a random independent perturbation, and therefore the offspring will have phenotype value

$$\mathbf{z} = \frac{\mathbf{x}+\mathbf{y}}{2} + \xi,$$

where ξ represents a random mutation term. Given s, t, ψ, and the distribution of ξ, the above relations permit the establishment of a recursion on the population density function p.

Gaussian Distributions. If the viability selection functions s and t, the preference function ψ and the random perturbations ξ are all Gaussian in form, then any Gaussian population distribution will remain Gaussian under the action of the recursion described above. In particular, let viability selection act on males according to the function

$$s(\mathbf{x}) = \exp\{-\langle(\mathbf{x}-\theta),\mathbf{S}(\mathbf{x}-\theta)\rangle/2\}$$

($\langle\alpha,\beta\rangle$ denote the inner product of the vectors α and β), and similarly on females according to

$$t(\mathbf{y}) = \exp\{-\langle(\mathbf{y}-\phi),T(\mathbf{y}-\phi)\rangle/2\}.$$

We will specify $s(\mathbf{x})$ and $t(\mathbf{y})$ to depend only on x_1 and y_2, respectively, taking

$$\mathbf{S} = \begin{pmatrix} s & 0 \\ 0 & 0 \end{pmatrix}, \theta = \begin{pmatrix} \theta \\ 0 \end{pmatrix}, \quad T = \begin{pmatrix} t & 0 \\ 0 & 0 \end{pmatrix}, \psi = \begin{pmatrix} \psi & 0 \end{pmatrix}. \tag{6.1}$$

We assume that the perturbing random variable ξ is Gaussian with uncorrelated components, mean zero, and variance components f and g.

For the special case $\psi(\mathbf{x},\mathbf{y}) = \exp\{-v(x_1 - y_2)/2\}$ and S and T (with $t = 0$) given in (6.1) where viability selection operates only on the character trait with the covariance matrix of $p(\mathbf{x})$ defined by

$$\Sigma = \begin{pmatrix} a & c \\ c & b \end{pmatrix}, \quad \Delta = ab - c^2, \tag{6.2}$$

we have the recursion

$$\begin{aligned} a' &= \{a + a\lambda + 2acv\lambda + a^2bv^2\lambda^2\}/4 + f, \\ b' &= \{b + b\lambda + 2bcv\lambda + bc^2v^2\lambda^2 \\ &\qquad + \lambda(s+v)\Delta\}/4 + g, \\ c' &= \{c + c\lambda + abv\lambda + c^2v\lambda + bcv^2\lambda^2\}/4, \end{aligned} \tag{6.3}$$

where the prime superscript denotes values in the succeeding generation, abbreviating the quantity $\lambda = 1/(1 + (v+s)a)$. (For the derivation of (6.3), see Karlin and Raper, 1990.)

It is clear that the equations (6.3) are increasing in b, so that the variation in female preference does exert a *disruptive* effect on the male character. An important question is whether Σ will converge to a finite limiting equilibrium. There are disruptive feedback effects that could cause instability and divergence at the covariance level. Conversely, the mechanism of midparental transmission having the effect of halving the variance each generation is a very strong factor in favor of convergence.

The principal result on the covariance dynamics:

RESULT 1. If $h(=\sqrt{g/f}) \le 1 + s/v$, where mutation in the preference variable is small or moderate compared to perturbation on the character variable, there is a unique positive-definite equilibrium Σ_∞ for the recursion of variance and covariance.

The case of $h > 1 + s/v$ is, in contrast, more variable. Numerical cases have been found where there are two covariance equilibria and where there are none. We present some simulation results.

(1) For $h > 1 + s/v$, there are either 0 or 2 finite equilibria.

(2) If there are no finite equilibria, then Σ followed over successive generations diverges to infinity.

(3) If there are two finite equilibria, then the smaller one is locally stable, the larger is unstable: the successive Σ either converge to the smaller equilibrium or else diverge to infinity.

(4) For $h \le 1 + s/v$, the unique finite equilibrium is locally stable. However, it is not globally stable; there are always initial values for Σ from which divergence to infinity occurs.

RESULT 2. When Σ diverges to infinity, then its components a, b, c increase geometrically at the same rate in the limit. Furthermore, $a{:}c{:}b$ are in geometric ratio in the limit, so that the correlation coefficient between character and preference, $\rho = c/\sqrt{ab}$, converges to 1.

This result demonstrates the manner in which divergence of Σ can occur: situations can arise in

which the preference and character are very closely correlated, and the former always has greater variance than the latter, which is sufficient that the resulting disruptive effect is more than the relative stabilizing power of viability selection. Result 2 entails that infinity always has a domain of attraction whatever the relative strengths of viability and sexual selection.

Dynamics of Mean Values

RESULT 3. (a) If $\sum_n$ diverges or converges to a limit that has $c/a > 1 + s/v$, then the sequence of population mean vectors does not in general converge. In this case, μ_n will move off at a geometrically increasing rate in a direction asymptotically approaching $\pm\begin{pmatrix} 1 \\ c/a \end{pmatrix}$.

(b) If $\sum_n \to \sum_\infty$ with $c/a < 1 + s/v$, then μ_n also converges.

Result 3 indicates that there is always the possibility that variation in female preference will prove so disruptive that the covariance matrix diverges to infinity. This is true however small the available power of sexual selection, as measured by $v > 0$, and however large the stabilizing power of viability selection. However, divergence will only occur if the mutational/segregation/environmental variance of the preference is sufficiently larger than that of the mutational/segregation/environmental variance of the male trait.

Result 3 involves a line of equilibria for the population mean values, a condition for its stability and the manner of convergence to it when it is stable (Karlin and Raper, 1990). There are conditions under which this line is unstable, namely when the coefficient of regression of preference on character is too high. This is *one way to interpret the runaway predicted by Fisher*.

In summary, Darwin (1871) and Fisher (1930, 1958) were motivated to explain extreme sexual dimorphism (e.g., spectacular male displays) in certain natural populations. Darwin invoked male competitive behaviors (e.g., combat, territorial defense) and female mating preferences (see Kirkpatrick, 1987, for a recent review on these behavioral patterns; see also Karlin and O'Donald, 1981; and O'Donald and Majerus, 1989, for refinements on mating selection forms). Pronounced sexually differentiated natural selection could also produce dimorphism, but this gives qualitatively different patterns. Fisher (1930) proposed a qualitative scenario "runaway process" of how extreme dimorphism can evolve starting with a slightly advantageous (viability) male phenotype selected for, engendering a correlated female mating preference more powerful than the viability factor and leading to more extreme male character displacement, eventually halted by counter natural selection forces. There are two types of runaway results, one on the metric trait, the second on the frequency domain of associated alleles. O'Donald (1967, 1980) presented simulations of a two-locus model pertinent to the frequency (allelic substitution) array runaway. O'Donald stressed the importance of the dominant or recessive nature of the underlying genotype and argued that, in this framework, evolution is generally slow and does not necessarily proceed at a geometric rate, contrary to the projections of Fisher's verbal theory. In Kirkpatrick's (1982) haploid model, it is suggested that preferred trait alleles can undergo frequency runaway in some cases, where there is an initial viability disadvantage which contrasts with Fisher's initial condition (see also O'Donald, 1990). We call attention to several recent finite multilocus theoretical studies of models incorporating both sexual selection (and mating selection) forces and viability selection (see Karlin and Raper, 1982; Raper, 1983; Lessard, 1986; O'Donald and Majerus, 1989; Christiansen, 1989a, b).

7. FISHER AND POLYGENIC INHERITANCE

The pioneering paper in this context is that of Fisher (1918) entitled "The correlation between relatives on the supposition of Mendelian inheritance." This paper was rejected by *Biometrika* (Pearson, editor) in 1916 and ultimately published in the *Transactions of the Royal Society of Edinburgh* (on this affair, see Joan Fisher Box, 1978).

Fisher's classic 1918 paper sought to establish a framework to account for continuous variation of metric traits in terms of Mendelian laws of inheritance with discrete Mendelian factors. This work introduced many seminal ideas and techniques including several key first steps in the development of the analysis of variance. In this presentation, the phenotypic variance of a trait, influenced by several loci subject to appropriate assumptions, is decomposed as a sum of independent "additive-genetic" and "dominance" variances plus an independent environmental variance. Fisher computed a number of phenotypic correlations of relatives as functions of the variance components and proposed to estimate components of variance from observed correlations and concomitantly to assess various heritability coefficients.

Fisher recognized the obvious necessity to take account of assortive mating. In looking for a rule of

mating that was tractable and meaningful, he proposed a mating function, but in the course of the approximations the analysis becomes difficult and obscure (cf. Kempthorne, 1957, Chapter 22). He effectively postulated time invariant marital correlations among spouses. Crow and Felsenstein (1968), Felsenstein (1981) and Feldman and Cavalli-Sforza (1977) also stipulated a time invariant correlation of mates, but none of these authors suggested any mechanism or process that explains how this correlation arises. It appears to be partly based on extrinsic factors not related to the population distribution of the polygenic trait.

It is unfortunate that, as Kempthorne (1977, page 722) has pointed out, the early works of Fisher [especially the 1918 paper, and perhaps Wright (1921a, b)] "had dominated thought ever since, and has perhaps limited the approaches of subsequent workers." It is awesome to recall that Fisher's paper was unconventional wisdom at the time. Kempthorne (1977) characterizes the Fisher 1918 paper as "remarkably difficult to understand so much that it is still under debate" (page 3). This work has been subjected to many exegeses. For example, Moran and Smith (1966) felt compelled to offer an annotated account with interpretations of the Fisher 1918 work. Further commentaries and alternatives on the frequency-dependent and selective nature of the assortative mating mechanism in the Fisher model occur in Kempthorne (1957, pages 492–493), Wilson (1973, 1978), Vetta and Smith (1974) and Karlin (1980a), among others.

Wilson (1973) endeavored to find a well-defined framework in which to justify the results of Fisher's assortative mating constructions. She underscores a number of apparent assumptions of Fisher that may be biologically problematic. For example, (1) the frequency of each allele is prescribed invariant over successive generations; (2) each individual has an equal probability independent of phenotype of being eligible to mate. This is called a "one-sided model." Wilson suggests a "two-sided model" and notes (even at equilibrium) that the variance of the children exceeds the variance of the parents.

The effects of selective assortative mating generally imply *non*-Hardy-Weinberg gene frequency distributions. The concept of additive genetic variance and breeding value is therefore not well defined. Kempthorne (1977, page 726) points out several of the ambiguities in the decomposition of variance when the frequencies of observations in the cells are *not proportional*. There is no natural way to define additive genetic variance for a *non*-Hardy-Weinberg population, especially in minimizing with respect to least squares (a procedure of which Fisher was so fond). Consider the case of a two allele trait with the following structure:

		A_1A_1	A_1A_2	A_2A_2
(7.1)	Phenotype values	I	J	K
	Genotype frequencies	P	$2Q$	R.

Assuming total mean effect as zero (i.e., $IP + JQ + KR = 0$) the additive deviation is taken (e.g., see Vetta, 1975) to be

$$(7.2) \qquad \frac{2(PI + QJ)}{p} \quad \text{and} \quad \frac{2(QJ + RK)}{q},$$

where $p = P + Q$, $q = Q + R$.

The above expression is not invariant nor does it provide any of the usual least square properties. The attempt to introduce additive (breeding) values α_1 and α_2 that minimize

$$L = P[I - 2\alpha_1]^2 + 2Q[J - \alpha_1 - \alpha_2]^2 + R[K - 2\alpha_2]^2$$

produces the value

$$(7.3) \qquad \hat{\alpha}_1 = \frac{q[PI + QJ]}{pq + Pq - pQ},$$

which reduces to (7.2) only if $P = p^2$, $Q = pq$, $R = q^2$, that is, when the population exhibits the Hardy-Weinberg proportions. This is in accord with observations of Kempthorne to the effect that the decomposition of variance has no natural representation in the situation of *non*-Hardy-Weinberg population frequencies. With multiple loci (say two) and phenotype values $\mu_{ij;kl}(i, j, k, l)$ traversing the allelic possibilities of locus 1(2), then, unless genotype frequencies are in global gametic equilibrium (i.e., $p_{ij;kl} = p_i^{(1)}p_j^{(1)}p_k^{(2)}p_l^{(2)}$), there is no natural and meaningful way to define additive genetic variance and dominance variance.

To sum up, under assortive mating with a metrical trait serious problems arise from: (a) the approximations in the treatment of nonadditivity; (b) the definitions and interpretations of additive genetic and dominance variances; (c) the lack of a meaningful analysis of variance for *non*-Hardy-Weinberg populations; (d) a hierarchy of conditional independence assumptions in the calculation of correlations of relatives; (e) linear relationships in regression of phenotype values on an individual or relative; (f) the independence of gene-environment interactions and lack of transmission of cultural components and their consequences on the biological variables; and (g) the assumption of constant within-sibship variance.

Perhaps completely new perspectives are called for and not modifications of the early approaches of

Fisher and Wright. Recently, advances have been made via the concept of selective mating functions. The method of selective mating functions does not impose conditional independence assumptions and can apply for extended family sets and pedigrees (see Karlin, 1979a, c; Wagener, 1976; Carmelli and Karlin, 1980).

What is the future of polygenic (multifactorial) inheritance? The problems of quantitative inheritance over the past two decades has re-emerged as a subject of intense activity. A broad spectrum of multifactorial polygenic models have been promulgated especially for purposes of evolutionary studies and for statistical objectives in genetic epidemiology and artificial selection programs. These models can be grouped into four categories: (1) polygenic models based on multiple alleles at many loci, (2) phenotypic transmission models without explicitly defining genotypic-phenotypic relationships, (3) biometrical approaches and (4) finite multilocus determinations.

Polygenic Models

Polygenic determinations generally postulate many additive allelic and loci effects that can be altered by mutations and environmental perturbations. Recent contributors to these studies include Kimura (1965), Lande (1975), Cavalli-Sforza and Feldman (1975), Fleming (1979), Nagylaki (1984), Turelli (1986), Turelli and Barton (1990) and others. There are differences among these models in the approximations and mathematical analyses used, in the assumptions made and in empirical adequacy. For convenience of tractability, most models on polygenic traits stipulate a Gaussian distribution of population phenotypes. This assumption is problematic since many physiological, biochemical, behavioral, and morphological quantitative traits are clearly non-Gaussian. Highly skewed phenotype distributions include lipids and lipoproteins, uric acid concentrations, body mass index, blood pressure readings, longevity (Sing and Skolnick, 1979; Rao et al., 1984), fiber strength in cotton, chicken egg count per year and egg size (Weir, Elsen, Goodman and Namkoong, 1988). Significant kurtosis occurs in measurements of human stature, human fetus birth weight and plant germination times. Multimodality is seen in the amount of phenylalanine in blood plasma (Penrose, 1951), coat color in mammals, fat content in raw milk, enzyme activity levels (e.g., taste thresholds in phenylthiocarbamide (PTC), red-cell acid phosphatase; see Cavalli-Sforza and Bodmer, 1971, Chapter 9). Many physiological variables entail strong nonlinear age dependence and show marked sex differences.

Among the reasons that many physiological and biochemical phenotype distributions are non-Gaussian, we emphasize three.

1. Many quantitative trait distributions are mixtures: major and polygenic components; different categories of normal and mutant genes contributing in diverse ways, some yielding extreme effects entailing rare phenotypes; polymorphism; and sample population heterogeneity.

2. The pervasive gene-environment interactions are a paramount source of non-Gaussian addends. Mixtures of genetic effects confounded with environmental influences often underlie multimodality.

3. Natural constraints: for example, stringent lower bounds but considerably more variable upper bounds occur with respect to blood pressure, body weight and heart rate. Limitations on one end of the character range would probably cause a skewed phenotype distribution; stringent constraints on both ends, a pronounced kurtosis.

Phenotypic Transmission Models

It is formidable, if not prohibitive, to accommodate interacting loci. However, study of the phenotypic changes due to mating pattern, parental or collateral transmission rules subject to nontransmitted environmental perturbations is reasonably tractable even in the non-Gaussian context. Apart from an integrity of its own, phenotypic variation modeling also offers insights concerning biological factors contrasted with cultural effects. Various models of phenotypic transmission motivated by genetic, ecological, and demographic phenomena occur in Slatkin (1970), Eshel (1971), Kingman (1980), Karlin (1979a-d, 1980), Bürger (1986) and others.

In simple quantitative terms, the dynamics of the population phenotype model involve two major stages: the mating (pair formation) process coupled to natural selection pressures and the parent-offspring transmission structure. A male and female x and y are joined by a preference (selection) process that is intrinsically nonlinear. For an established parental couple $(\tilde{x}, \tilde{y})$, a male offspring acquires a phenotype value of form $x' = R(\tilde{x}, \tilde{y}) + \underset{\sim}{\epsilon}^{(m)}$, where R is a transformation of the parental values and ϵ conveys a residual (random-environmental) contribution independent of the parental phenotypes. For a female offspring, the analogous transmission rule is $y' = S(\tilde{x}, \tilde{y}) + \underset{\sim}{\epsilon}^{(f)}$, where S may differ from R.

Biometrical Studies of Quantitative Inheritance

These include path analysis (linear) models (e.g., used extensively in genetic epidemiology; see the

edited volumes of Sing and Skolnick, 1979, and Rao et al., 1984), variance decomposition and regression methods (Cockerham, 1954), and nonparametric methods (e.g., Karlin and Williams, 1984).

Multilocus and Major Gene Models

A second important category of continuous trait models recognizes an underlying *major gene* (or a few genes) involving a number of alleles with corresponding genotypes whose expression traverses a wide range of phenotypic values. The variability in the expression of a genotype is contributed to by a complex of genetic and environmental heterogeneous influences. The key ingredients of the major gene models can be summarized as follows: (1) genetic factors controlled at the major loci produce large effects relative to the phenotypic standard deviation; (2) other genetic and environmental factors and/or errors of measurement cause a continuous phenotype expression; and (3) segregation is Mendelian for the major loci. The foregoing model has been used for problems of animal and plant breeding in investigating the consequences of various artificial selection protocols. Also, extensive biometrical and statistically oriented studies in family and pedigree analyses reflect current efforts to demonstrate the major gene factors that play a significant role in multifactorial diseases (e.g., Sing and Skolnick, 1979, Chapter 23; statistical approaches are reviewed in Lalouel, Rao, Morton and Elston, 1983, and Bonney, 1984). The extension of the theory on major gene models to accommodate selective assortative mating mechanisms is considered in Carmelli and Karlin (1980).

The recent (1987) extensive conference on quantitative genetics in all its ramifications and the consequent voluminous conference volume (Weir, Elsen, Goodman and Namkoong, 1988) offer much theoretical and applied information and challenging issues for future research in the agricultural, health and basic biological enterprise.

8. PERSONALITY, IDIOSYNCRASIES AND LEGACY OF R. A. FISHER

Fisher accepted a Professor Chair (of Genetics) at Cambridge only after WWII. This opened opportunities for formal experimental work to complement his theoretical and field data studies. With respect to his experimental efforts, Fisher was very interested in recombination (phenomenon of crossing over). For lack of space, he set up a laboratory in his home (also the lodge of his department) to study recombination primarily in the mouse. The large garden of the genetics department laboratory was converted to a plant breeding station (Cavalli-Sforza, 1990). Here he cultivated the Mendel varieties of peas and generally was intrigued by problems of polyploidy (see Section 2) in plants. His book *The Theory of Inbreeding* (1949) underscores problems stimulated by his horticulture practices. Earlier Fisher (1941) investigated extensively theoretical genetic models of incompatibility systems and self-sterility mechanisms in plant species.

Because of enthusiasm for linkage and recombination and recognizing its importance in the genetics of human diseases, he proposed the construction of a human genetic map 40 years prior to the present human genome initiative. From data provided to him he characterized the single dominant gene nature of the Huntington's chorea syndrome. He also predicted new Rh antigenic variants based on a 3-locus tightly linked cystron (1947), which were later confirmed experimentally. Fisher's greatest contributions to evolution and genetics were theoretical; he was best with intuition and informal mathematical insights supported by computations done on his desk calculator.

Fisher had idiosyncrasies. His relations with other scientists were either intensely positive or intensely negative. Because of bad relations with K. and E. Pearson, he helped found the Biometric Society and its journal as a competitor to *Biometrika.* Fisher was an uncompromising eugenicist; he wrote many articles espousing strict controls on human marital prerogatives and was very active in the British Eugenics Society, inter alia, serving as major editor of *Annals of Eugenics* for many years. Especially fascinating are the letters of Fisher on topics of heredity and eugenics (see Bennett 1983), including selected correspondence with Leonard Darwin. Fisher and others (especially Haldane) discussed short- and long-term fitness relationships as the biological bases of social behavior. Fisher (1930) devoted three chapters to qualitative modeling proposals concerned with social hierarchies and their place in human evolution. In parallel discussions, he examined cases of evolution of distasteful qualities in insect larvae, mutual interaction between parental care and fertility in social insects and humans and social selection for fertility in human tribal societies. In these contexts he, as other more recent evolutionists, emphasized the roles of kin and group selection. Despite the overwhelming evidence on the dangers of smoking (e.g., lung cancer), Fisher associated the deleterious health aspects of smoking exclusively to genetic dispositions. Fisher's relationships with other major evolutionists and statisticians were frequently combative. This is manifest in his polemic writings and verbal disputations with

Haldane and Wright. Each of these giants tried to surpass the others, thus illustrating the Talmudic adage "jealousy of scribes increases wisdom."

Students of Fisher

Fisher did not have many students (apparently only one in statistics), but the few he had were superb. We mention five.

(1) J. H. Bennett studied evolutionary models of multilocus systems. He recently edited a five-volume collection of Fisher's papers.

(2) C. R. Rao is, over the past four decades, among the leaders worldwide in pure and applied statistics.

(3) P. O'Donald extensively researched sexual selection in many forms.

(4) A. W. F. Edwards studied adaptive models of sex ratio evolution and wrote a book on *Likelihood.*

(5) Sir W. F. Bodmer is among the world's leading molecular biologists. He has contributed broadly and incisively to evolutionary theory, immunology and cancer genetics.

Genetic Associates of Fisher

(1) L. Cavalli-Sforza (post-doc. 1948 to 1950) ranks among the leading human geneticists.

(2) K. Mather made important contributions on recombination models. He also authored a well-known text on *Statistical Analysis in Biology* (1966).

(3) A. R. G. Owens taught in Fisher's department and helped develop mathematical models of recombination based on renewal stochastic processes.

(4) E. B. Ford, a frequent collaborator of Fisher, helped characterize genetic polymorphisms of melanism and mimicry in moths and butterflies.

(5) R. Race, a great friend, much influenced by Fisher, was among the first to classify human blood groups and their distribution and with R. Sanger wrote a definitive early book on human red blood cell typings.

(6) A. Mourant, with the advice of Fisher, established a detailed data base of protein polymorphic frequencies of humans.

(7) D. J. Finney, interacting with Fisher, studied models of sex incompatibilities in plant populations and wrote a text on the practice of biological assays.

All of these students and associates are gems of Fisher's legacy.

Given his interest in evolution and statistics, on what would Fisher's efforts focus were he alive today? My personal surmise is that on the experimental side he would labor hard as a molecular geneticist and certainly be a key player in the Human Genome Initiative (like his student Sir W. F. Bodmer). On the theoretical side, the computer in all its embellishments would serve his intuition.

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