Potential Germline Competition in Animals and Its Evolutionary Implications

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ABSTRACT

Mutation, mitotic crossing over and mitotic gene conversion can create genetic diversity in otherwise uniform diploid cell lineages. In the germline this diversification may result in competition between diploid germline phenotypes, with subsequent biases in the frequency of alleles transmitted to the offspring. Sperm competition is a well documented feature of many higher organisms and a model is developed to quantify this process. Competition, and hence selection, can also occur by differential survival of diploid lineages before meiosis. It is concluded that under certain circumstances germline selection is an efficient means of eliminating unfavorable alleles from the population. This does not require differences in adult fertility or viability which is the usual mechanism cited as causing changes in gene frequency in a population. It is proposed that such competition may play a role in maintaining the efficiency of basic metabolic pathways.

THE phenomenon of gamete competition in plants has been considered and documented [MULCAHY (1975); but see CHARLESWORTH, SCHEMSKE and STORK (1987)]. This is possible because plant gametes express their haploid genotype. One adult plant produces a population of different haploid phenotypes with the potential for competition to occur between them. In contrast animal germline cells appear only to transcribe their diploid genotype. The haploid gametes appear transcriptionally silent and function using the metabolic machinery inherited from their diploid progenitor (SIVINSKI 1984). Thus animal germline cells must be functionally identical, all being a product of the adult diploid genotype. This is demonstrated by the ability of *Drosophila melanogaster* sperm to function normally even when nearly devoid of DNA (LINDSLEY and GRELL 1969). Competition between (identical) animal gametes therefore cannot occur and its potential has been largely ignored.

However, this line of reasoning ignores the molecular processes that create diversity in diploid cell lineages by mutation and genetic exchange by mitotic crossing over and mitotic gene conversion. The analysis presented here will investigate whether these processes can create sufficient diversity for selection between *diploid* genotypes to occur.

MODEL DESCRIBING DIPLOID CELL LINEAGE DIVERSIFICATION AND SELECTION

The meiotic products of diploid cells, the gametes, are considered to be metabolically passive copies of their diploid progenitor cell and to contain a random haplotype, *i.e.*, a heterozygous progenitor will produce a 1:1 ratio of gametes containing each allele. The model will consider selection in only one sex, the male, by sperm competition, while the female germline is not considered to undergo selection. This is the simplest, most rigorous case and allows widespread applicability even to large mammals where millions of sperm may compete for only one egg. A simple two allele model will be considered where A and a represent the two alleles. The molecular processes can be represented as follows: μ is the mutation rate from A to a, μ_r is the reverse mutation rate from a to A and X is the rate of unbiased mitotic crossing over and unbiased mitotic gene conversion. Note that X represents not only mitotic crossing over plus gene conversion but any molecular process that results in reciprocal exchange between homologous chromosomes. This creates diversity in germline cells as shown in Table 1.

The relative fitness of the germline cells is defined as $AA = 1$, $Aa = 1 - hs$ and $aa = 1 - s$, where s is the selection coefficient against the homozygote aa, and h is a measure of dominance. If we define the initial frequencies of A as p and a as q, the initial adult genotype frequency of AA is p^2, Aa is $2pq$ and aa is q^2.

The frequency of A gametes derived from males in the next generation is calculated as follows:

$$\begin{aligned}\text{Frequency} = &= p^2\{(e_{11}) + 0.5\,(e_{21})(1 - hs)\}/ \\ &\{(e_{11}) + (e_{21})(1 - hs)\} + 2pq\{(e_{12}) \\ &+ 0.5(e_{22})(1 - hs\}/\{(e_{12}) + (e_{22})(1 - hs) \\ &+ (e_{32})(1 - s)\} + q^2\{0.5(e_{23})(1 - hs)\}/ \\ &\{e_{23}(1 - hs) + (e_{23})(1 - s)\}\end{aligned} \quad (1)$$

TABLE 1

Conditional genotype probabilities produced within parental genotypes by mutation from *A* to *a* (μ), mutation from *a* to *A* (μ_r) and genetic exchange between homologous chromosomes (*X*), assuming that μ, μ_r and *X* are sufficiently small that second order terms can be ignored

	Parental genotype		
Germ cells	*AA*	*Aa*	*aa*
AA	$1 - 2\mu$ (e_{11})	$\mu_r + 0.5X$ (e_{12})	0 (e_{13})
Aa	2μ (e_{21})	$1 - \mu_r - X - \mu$ (e_{22})	$2\mu_r$ (e_{23})
aa	0 (e_{31})	$\mu + 0.5X$ (e_{32})	$1 - 2\mu_r$ (e_{33})

The probabilities can be regarded as components of a matrix, designated (e_{11}) to (e_{33}), and used to clarify Equation 1 in the text.

and the frequency of gametes derived from females is as in (1) above except that $s = 0$.

This equation gives the proportion of *A* gametes produced by each adult genotype and weights them by the relative frequency of their adult genotypes. It therefore assumes no differences in fertility between the three adult genotypes.

In the absence of a precise solution for this equation the equilibrium values of *A* and *a* were calculated using an iterative computer program incorporating appropriate values for the parameters. Such a program also yields information on the dynamics of the process, which was assumed to have reached equilibrium when the proportionate change in gene frequency over one generation was less than 2×10^{-8}. The program calculated gene frequencies transmitted through each sex and used them to calculate adult genotype frequencies in the next generation. This avoids problems inherent in assuming Hardy-Weinburg equilibrium when the sexes have differing gene frequencies. The program was run for different parameter sets and typical results are illustrated in Figures 1 and 2. Values of *X* below 10^{-4} were not considered since the process is slow, large amounts of computer time are involved, and the equilibrium levels of the favourable allele are low.

The process can be visualized as acting in three stages: mutations (μ) create new variants within the population and/or individual, DNA exchange and conversion mechanisms (*X*) generate a range of diploid genotypes within the germline and subsequent competition and selection (*h* and *s*) operates to eliminate the less beneficial allele. The end product of the process is therefore the result of the interplay between these four parameters μ, *X*, *h* and *s*. Simulation studies (Table 2, Figures 1 and 2) suggest that *X* is the critical parameter, since the diversity generated by *X* is directly responsible for the subsequent competition. The model appears relatively insensitive to changes in *h* and *s* at levels of *X* greater than 10^{-3}, and particularly insensitive to changes in *h*, an interesting result when applied to selection on biochemical pathways

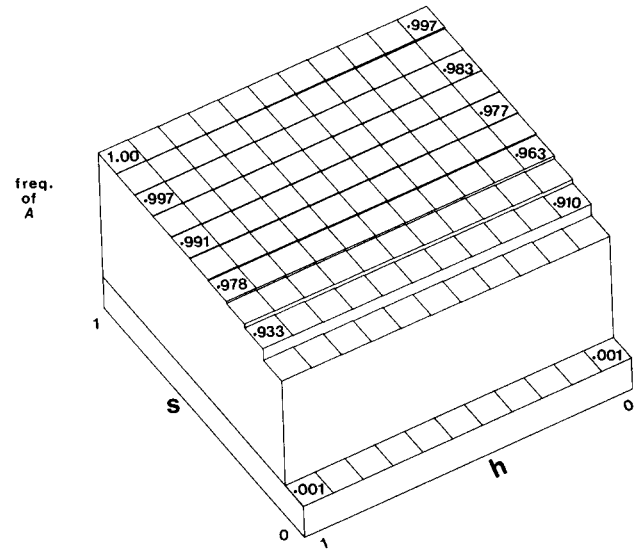

FIGURE 1.—Effects of changing parameters "*s*" and "*h*" on the equilibrium frequency of *A*. *X* is 10^{-3}, μ is 4×10^{-6} and μ_r is 4×10^{-9}. The value of *s* is varied from 0 at the front to 1 at the rear in increments of 0.1. The value of *h* is varied from 1 on the left to 0 on the right, in increments of 0.1.

(see later). Figure 2 illustrates the effect of changing *X* and μ while holding *h* and *s* constant and is a typical result over a range of *h* and *s* values. The mutation rate μ appears influential at lower levels of *X* but becomes increasing less important at higher levels when sufficient germline diversity is generated to allow effective selection to operate against the unfavorable allele. Although there appears to be no simple algebraic solution for the equation, it is possible to make some assumptions and derive approximate expressions to describe the process (see APPENDIX). The formulae support these results by showing that at high values of *X*, the equilibrium value of *A* will also be large; μ and *s* affect the equilibrium but at the levels of *X* considered here their contributions are swamped in absolute (but not relative) terms.

The dynamics of the process are illustrated graphically for a range of parameter values in Figure 3. Although *X* is the critical equilibrium-determining factor, *h* and *s* influence the speed at which this equilibrium is regained after perturbation.

The slow rate of change may make the process vulnerable to the effect of drift in small populations when the adult stage of the life cycle acts as a bottleneck. The magnitude of drift effects will depend on the adult effective population size and subsequent recovery from perturbations will depend on the size of parameters *X*, *h*, μ and *s*. An approximate expression for this rate of recovery is derived in the appendix and appears to fit the observations as shown in Figure 3.

When compared with selection against adult phenotypes [$p = 1 - 2\mu/s$ for $h = 0.5$, $p = 1 - (\mu)/hs$ for $h = 0.02$, $p = 1 - (\mu/s)^{0.5}$ for $h = 0$, CROW (1986)],

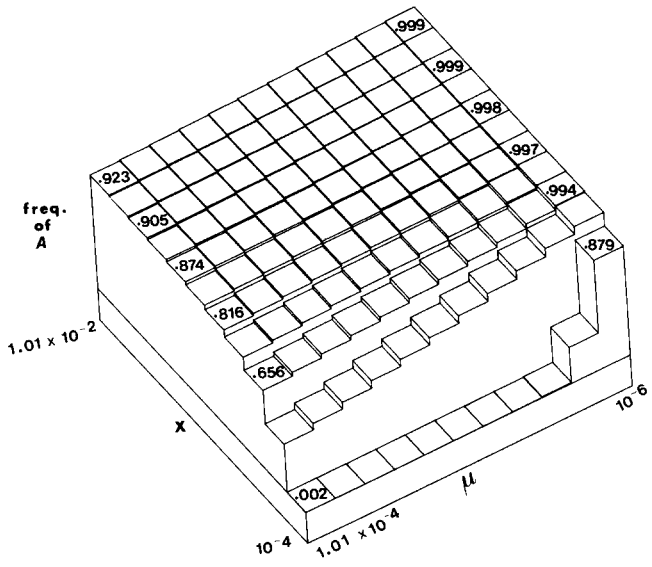

FIGURE 2.—Effects of varying the parameters "X" and "μ" on the equilibrium frequency of A when s is 0.5 and h is 0.02. The value of X is varied from 10^{-4} at the front to 1.01×10^{-2} at the rear in increments of 10^{-3}. The value of μ is varied from 1.01×10^{-4} at the left to 10^{-6} on the right in increments of 10^{-5}; μ_r is $\mu \times 10^{-3}$.

the model was less effective at screening out the unfavourable allele; see Table 2. There is of course no reason why the two processes cannot act simultaneously. Their relative contributions would depend on the magnitude of the relevant parameters.

The model does not apply to genes coded by the mitochondrial genome which are transmitted maternally and are governed by the processes of clonal selection and drift. Enzymes that function in the mitochondria but are coded by the nuclear genome (*e.g.*, enzymes of the Krebs cycle or electron transport chain) are described by this model, since their site of expression is immaterial. In many species with differentiated sex chromosomes, genetic exchange does not occur between the two sex chromosomes. When males are the heterogametic sex, no opportunity exists for genetic exchange between sex-linked loci during sperm formation and the value for X is zero. Sex-linked genes may be subject to a mutation/selection balance within the germline but the value of s would have to be considerably higher to achieve an equilibrium favouring allele A. The model only considers selection in one sex, but if selection occurs in both sexes, genetic exchange (X) in the homogametic will result in the same equilibrium frequencies obtained above. Selection in the adult phase of the life cycle may be sufficient to eliminate deleterious sex-linked genes since by definition these loci will be dominant in the heterogametic sex.

PARAMETER VALUES FOR THE MODEL

The parameters X, μ and μ_r describe diversity within germline cells immediately prior to meiosis. They represent cumulative totals of these processes over the cell divisions prior to meiosis. Mitotic crossing over is a well documented phenomenon (WHITEHOUSE 1982) but there are no reliable estimates of its frequency. Mitotic gene conversion has been observed in yeasts but its frequency in higher organisms is unknown (JOHN and MIKLOS 1988). Any mechanism of reciprocal exchange between homologous chromosomes is represented by the term X. The value of X is essentially guesswork but testis is a rapidly dividing tissue and gametes are the product of a larger number of cell divisions than somatic tissue. The value of X in germline tissue may therefore be much higher than that estimated for the soma. Mitotic crossing over appears to occur even in the absence of meiotic crossing over, for example in males of higher Diptera. GETHMANN (1988) in a recent review concluded that "mitotic, or somatic crossing over probably occurs at a low frequency in all Diptera"; the estimates of its frequency were in the region 2×10^{-4} to 1×10^{-3}. Mutation rate per enzyme coding region per gamete is usually regarded as around 10^{-5} although the best estimate for *D. melanogaster* is 4×10^{-6} (VOELKER, SCHAFFER and MUHAI 1980). Mutations restoring enzyme activity are estimated to be 1000 times less frequent than those destroying activity in bacteria (FREIFELDER 1987). Since enzyme structure and function are similar in all organisms it is possible to estimate μ_r as $\mu \times 10^{-3}$. The dominance index "h" is likely to be small due to the properties of biochemical pathways described later. The magnitude of these parameters suggest that biases in the transmission frequency are likely to be small. Assuming $X = 10^{-3}$, $\mu = 4 \times 10^{-6}$, $\mu_r = 4 \times 10^{-9}$, $h = 0.02$ and $s = 0.9$ (resulting in an equilibrium frequency of $A = 0.981$; table 2), the frequency of A gametes transmitted by an Aa individual will be 0.50023; such small biases will be invisible in most experimental protocols.

Estimates of sperm competitive ability are available for several mammalian species. COHEN and Mc-

TABLE 2

Equilibrium frequency of A due to selection on germline or adult phenotype, assuming $\mu = 4 \times 10^{-6}$ and $\mu_r = 4 \times 10^{-9}$

s	h	Germline selection				Adult selection
		X				
		10^{-1}	10^{-2}	10^{-3}	10^{-4}	
0.9	0.50	1.000	0.999	0.991	0.992	1.000
	0.02	1.000	0.998	0.981	0.814	1.000
	0.00	1.000	0.998	0.980	0.810	0.998
0.5	0.50	1.000	0.997	0.976	0.753	1.000
	0.02	1.000	0.996	0.965	0.652	1.000
	0.00	1.000	0.996	0.964	0.647	0.997
0.1	0.50	0.998	0.983	0.828	0.006	1.000
	0.02	0.998	0.982	0.818	0.005	0.998
	0.00	0.998	0.982	0.817	0.005	0.994

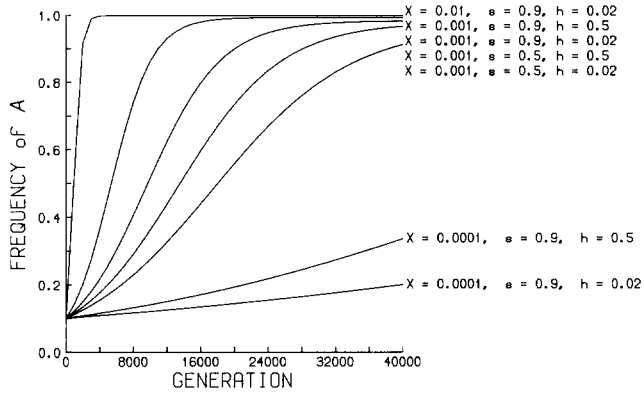

FIGURE 3.—Effects of changing parameters X, s and h on the dynamics of gene frequency change attributable to germline competition. μ is 4×10^{-6} and μ_r is 4×10^{-9}.

NAUGHTON (1974) mated rabbits and later recovered sperm from several regions of the reproductive tract. The recovered sperm were used to inseminate other rabbits and the number required to produce a pregnancy was estimated. On average 100 sperm from the oviduct, 80,000 from the uterus or 4×10^6 fresh sperm were sufficient to cause pregnancy; giving rise to a potential value of s as high as 0.999975. This may also reflect differences in the physiological maturation of the sperm but the experimental conditions were designed to favour the fresh sperm. In any case it demonstrates the enormous potential for sperm competition which exists *within* an individual irrespective of its biochemical or physiological basis. BEATTY (1975) cites experiments designed to measure sperm competitive ability between strains of mice, rabbits and cattle. Fertilizing ability differed by a range of factors up to 12, 12 and 27, respectively, but these represent differences between genotypes rather than differences generated within an individual. Although these reports cannot give definitive figures for the value of "s," the selection differentials of sperm within an individual, they provide a guide as to their potential magnitude.

GERMLINE CELL METABOLISM

The process of germline competition predicted above can maintain a high frequency of advantageous alleles in the face of persistent mutation pressure. The question is whether these alleles are specific to sperm function or of more general metabolic interest.

Biochemical studies of sperm are relatively recent and mainly concerned with mammalian systems (BLUM 1986; ZANEVELD and CHATTERTON 1982). Sperm express the enzymes necessary for the oxidation of fatty acids, glycolysis, Krebs cycle, electron transport, oxidative phosphorylation, and possibly the hexose-monophosphate shunt. Evidence also points to their synthesis of lipids and glycogen while stored in the testes. Thus all the major biochemical pathways appear to play a role in sperm metabolism. During internal fertilization the ability of the sperm to reach the egg is dependent largely on its ability to convert metabolites into motility. The metabolites come either from its surrounding fluids which contain sugars, amino acids etc. (selection on the degredative pathways) or from its internal stores of lipid and glycogen (retrospective selection on the synthetic pathways). Although passive transport of sperm may occur in some mammalian species by smooth muscle contractions of the uterus etc., their own motility still plays a large part. It is possible that sperm must move to avoid depletion of nutrients within its immediate vicinity (PETERSON 1982), this would add an "amplification" step to the process in the form of positive feedback i.e. the more motile sperm gain more nutrients which further increases their motility.

Sperm motility is the most obvious physiological process affecting fitness but is not the only one. Any processes acting in the cell lineage which affect viability generate selection pressures on enzymes not normally expressed in sperm such as DNA synthesising and repair enzymes, ribosomal proteins etc. For example, mutation of an enzyme involved in DNA replication may increase a cell's doubling time, reducing its fitness in an environment of clonal expansion and selection. This situation is analogous to bacteria in a chemostat except that diploid cells are considered and diversity is created not only by mutation but also by mitotic crossing over and gene conversion. The model can describe this process simply by altering the definition of the selection coefficient "s." Diversification within the germline described earlier assumed that no selection occurred before the final meiotic division, biases in transmission frequency being a result of subsequent differences in sperm competitive ability as described by the parameter "s." In the case of germline clonal competition the bias arises *before* the final meiotic division as a result of differential survival of lineages. This differential survival can also be represented by the parameter "s," which in this case describes the selection coefficient accumulated over the cell generations prior to meiosis. This type of competition can occur in the diploid lineages of both sexes, resulting in much higher equilibrium frequencies of the favoured allele (but note that in mammalian females the final meiotic division occurs very early in development). It is therefore possible that germline competition plays a role in the maintenance of efficient metabolic machinery, even before the final meiotic division forms the haploid germ cells. This makes the process applicable to mating systems where direct sperm competition is likely to be of minimal importance compared to chance events, such as the mass release of eggs and sperm into water. In these organisms the ability of diploid cell lineages to survive

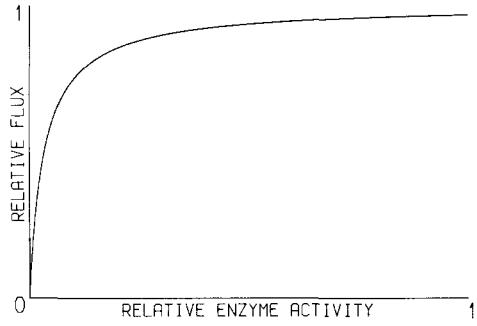

FIGURE 4.—Effect on flux through a biochemical pathway due to changing the activity of one constituent enzyme. After KACSER and BURNS (1981).

and flourish in the reproductive sacs prior to release will result in the biases predicted above. Once such a process has started even in a rudimentary form, it has the impetus to persist and develop given the marginal cost to the adult of within-germline competition and the benefits of passing on a more efficient basic metabolism.

METABOLIC PATHWAYS IN GERMLINE CELLS

The model derives circumstantial support from recent work examining the influence of individual enzymes on biochemical pathways. These theoretical and empirical investigations found a law of diminishing returns as shown in Figure 4 (KACSER and BURNS 1981). This states that the activity of an enzyme may fluctuate widely with a negligible effect on flux; even the 50% reduction in a wild type/null heterozygote has a negligible effect on phenotype as demonstrated by the fact that the wild type allele is invariably dominant. HARTL, DYKHUIZEN and DEAN (1985) summarized these studies and applied them to population genetics. Using data from *D. melanogaster* they calculated that most metabolic enzymes were located along the plateau of Figure 4. They deduced that enzyme variants spread along this plateau are effectively neutral since the value of $4N_e s$ is considerably less than one, where N_e is effective population size and s is the relative selective disadvantage of an allele, in this case taken as equivalent to its effect on flux. In effect they are below the level of resolution possible by natural selection. An appraisal of these approaches leads to a dilemma not usually acknowledged in evolutionary theory. Enzymes are exceedingly efficient and in some cases approach "catalytic perfection," the stage at which the rate of catalysis is limited by the rate of diffusion bringing substrates into contact with the enzyme molecule. This efficiency is maintained across species and through generations in the face of repeated mutations. The vast majority of mutations will result in decreased catalytic efficiency and it is obvious that some selective pressure(s) must be maintaining them at this level of efficiency. However as pointed out, natural selection as usually envisaged lacks the degree of resolution necessary to achieve this.

A critical assumption in this analysis is that flux equals fitness. This is unlikely to be true in the adult multicellular phenotype where complex physiological systems have evolved to regulate biochemical pathways. In adults, flux is determined not only by individual enzymes but also by higher processes of homeostasis such as hormonal regulation which modulate their activity. In this situation, maximum fluxes are less likely to be critical parameters affecting fitness. This may explain the results of VOELKER *et al.* (1980) and LANGLEY *et al.* (1981) who found no differences in fertility or viability between adults homozygous or hemizygous for near-null enzyme mutations and their wild-type counterparts in *D. melanogaster*, a result later confirmed by BUKHART *et al.* 1984. Similar results are reported in O'BRIEN and MACINTYRE (1978). In contrast, germline cells appear critically dependent on their basal metabolic pathways and maximum fluxes determine fitness to a larger extent than in adults. Selection pressures acting on individual enzyme activities will therefore be higher in this stage of the life cycle. The problem remains as to the ability of germline competition to discriminate between enzyme variants with only a marginal effect on flux. This problem exists only if we continue to regard flux as equivalent to fitness. As stated earlier, sperm motility may have a positive feedback effect since more motile sperm avoid local depletion of nutrients; this phenomenon will generate larger differences in fitness between genotypes than predicted by consideration of flux alone. In the case of competition between different germline lineages it is possible that flux equals fitness at the level of individual cells, but small differences in fitness act cumulatively to create increasingly large fitness differences over a number of cell generations. These mechanisms amplify the small fitness differences associated with flux to the extent that selective pressures may be able to discriminate between enzyme variants with only minor changes in activity.

A feature of this process of germline competition is that selection occurs as an endogenous property and, unlike normal selection/mutation models, does not require differences in fertility or viability between adult phenotypes, a feature more in line with empirical observations. Given the assumptions that germline cells are critically dependent on their basic metabolic machinery, that molecular processes create diversity in the germline and that competition occurs between gametes or lineages, it is possible to generate large selection pressures acting on biochemical pathways. It offers a solution to the problems raised by recent studies on the effects of enzyme mutations on bio-

chemical pathways and their apparently negligible effects on adult phenotypes.

EVOLUTIONARY IMPLICATIONS OF GERMLINE COMPETITION

If the model accurately represents processes occurring in the germline it has implications for evolutionary theory beyond the maintenance of enzyme efficiency. It implies that some enzyme variants are selected to compete in the internal conditions of the reproductive tract and are effectively buffered from the external environment. Attempts to correlate certain enzyme variants with clines of environmental variables are likely to be unrewarding with the possible exception of temperature clines in poikilotherms. It predicts a possible conflict of interests between germline and adult phenotypes in the maintenance of enzyme efficiency. Advantageous phenotypic changes in the adult may be achieved by decreasing the efficiency of enzymes, *e.g.*, decreased fat content by mutations in the fat synthesising pathway, but such enzymatic changes might be selected against in the germline. This conflict suggests that evolutionary change may occur not by modulation of enzyme activity but by mutations in genes involved at higher levels of physiological control in adults, such as hormones or hormone receptors, and explains why enzymes are functionally so similar even between species of widely divergent phenotype.

Differences in competitive ability can be observed directly as the meiotic drive systems known in many species. These appear to result from physiological disruption of meiotic divisions eliminating the sensitive alleles rather than by a biochemically more efficient metabolism. They are prevented from spreading to fixation by their deleterious effect when homozygous, *i.e.*, are genes of large phenotypic effect. DAWKINS (1982) suggested that segregation disorders may be more common than realized since only those with large phenotypic effects will be noticed; those involving small quantitative effects of the type envisaged here are largely invisible. It is tempting to speculate that such genes first arose by eliminating those lineages in the germline which did not contain a copy i.e. in a heterozygote *Aa* individual, where *A* is the driven gene, lineages of type *aa* would be eliminated with a subsequent bias in the transmission frequency of *A*. Once started evolution would increase their segregating ability and their frequency would increase until fixation (if no deleterious effects) or until balanced by selection against the homozygote. Considerations of segregation disorders must be speculative because of their different underlying physiology but it is encouraging to note that biases in transmission frequency do occur in nature as predicted by the model, albeit under different circumstances.

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APPENDIX

Derivation of some simple approximations for Equation 1

In the following it is assumed that the frequency q of the mutant type a is sufficiently small that terms in q^2 can be ignored relative to q. The frequency of a gametes transmitted from AA males is:

$$q'_{AA} = \mu(1 - hs)/(1 - 2\mu hs) \simeq \mu(1 - hs).$$

Similarly for Aa males:

$$q'_{Aa} = [(1 - \mu - X)(1 - hs)/2 + (\mu + X/2)(1 - s)]/[(1 - hs(1 - \mu - X) - s(\mu + X/2)]$$

which if we also consider s to be small and disregard higher order terms reduces to:

$$q'_{Aa} \simeq (1 + \mu - \mu s - Xs/2)/2.$$

For q small we can approximate the adult genotype frequencies of AA as $1 - 2q$ and Aa as $2q$. Thus:

$$q' = (1 - 2q)\mu(1 - hs) + q(1 + \mu - \mu s - Xs/2)$$
$$= q(1 - \mu - \mu s + 2\mu sh - Xs/2) + \mu - \mu hs.$$

In females the same equation applies but with $s = 0$. Thus the mean frequency transmitted through both sexes is:

$$q' = q + q(2\mu sh - 2\mu - \mu s - Xs/2)/2 + \mu - \mu hs/2.$$

At equilibrium $q' = q$ and, ignoring deviations from Hardy-Weinburg equilibrium the equilibrium frequency of q, represented by q_e is:

$$q_e = \mu(1 - hs/2)/[s(X/2 + \mu - 2\mu h)/2 + \mu].$$

Consider some special cases:

For $h = 0$: $q_e = \mu/[s(X/2 + \mu)/2 + \mu]$

For $X \gg \mu$: $q_e = \mu(1 - hs)/(sX/4)$

For $X \gg \mu$ and h or s small: $q_e = 4\mu/sX$,

which is analogous to selection against the adult ($q = \mu/hs$ for partial dominance) since the equation can be rewritten as $q = (2\mu/s)/(X/2)$.

The effects of drift

From the previous section, the expected change in terms of the equilibrium frequency can be shown to be:

$$\delta q = -(q - q_e)(\mu - \mu hs + \mu s/2 + Xs/4)$$

which if s is small and $X \gg \mu$ reduces to:

$$\delta q = -(q - q_e)(\mu + Xs/4).$$

The variance among lines due to drift is given by $q(1 - q)/2N$ approximately, where N is the effective population size, which for small q approximates to $q/2N$. Thus the final variance about the equilibrium value will depend on the relative values of $1/N_e$ for the adult population and the terms X, μ, h and s operating in the germline; it can be shown that when q is small this variance will equal q_e/Nsx.