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COMMENTARY

Why are most mutations recessive?

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Abstract. It is a long-standing observation that most mutations are recessive. That is, they do not lead to visible phenotypic effects when in heterozygous combination with the wild-type allele. The reason for this has long been debated. Fisher (1930) attributed the observed dominance of the wild type to the action of natural selection at modifier loci. Wright (1929) on the other hand asserted that dominance did not have a selective function *per se*, but was a more-or-less automatic offshoot of genetic regulatory mechanisms. The present essay discusses these explanations from a contemporary standpoint and suggests that neither is likely to be valid exclusively. In particular, even when physiology appears to offer a sufficient explanation, evolution of dominance cannot be ruled out.

Keywords. Dominance; recessiveness; evolution.

Almost every decade the question of the evolution of dominance is 'definitively' settled by one or another evolutionist, only to emerge again as a difficult issue.
– W. B. Provine (1992)

1. Introduction

When Mendel intercrossed true-breeding pigmented and unpigmented forms of his pea, he found that the progeny were all pigmented. On self-pollinating the progeny, 705 out of 929 plants yielded pigmented seed coats and flowers and the remaining 224 were white (Mendel 1865). His explanation for this was, in part, that 'those characters which are transmitted entire, or almost unchanged by hybridization, and therefore in themselves constitute the characters of the hybrid, are termed the dominant, and those which become latent in the process, recessive' (translation in McKusick 1992). In effect, Mendel said that true-breeding traits were embodied in discrete units; an individual plant contained a pair of such units for each trait. When the traits were dissimilar, one of them could override the effects of the other. Such a trait was defined to be *dominant* to its partner, which was called *recessive*. The nomenclature, which survives to this day, pertains only to traits or phenotypes and has nothing to say about consequences for fitness. The question that concerns us is: Why are some traits dominant to others? Specifically, why are most mutations recessive to the prevailing wild type (table 1)? Is it that natural selection specifically favours the dominance of the wild type, or is dominance a fall-out, as it were, of selection acting on entirely different but correlated aspects of organismal phenotype? Or might selection not be involved at all? The aim of this essay is to present a limited and somewhat discursive discussion of dominance and recessiveness. My aim is, firstly, to draw attention to an intriguing problem and to the analysis to which it has been subjected by many of the leading contributors to the evolutionary synthesis. Secondly,

I wish to suggest that this is an issue whose resolution will demand the mutual accommodation of apparently conflicting attitudes.

Whether dominance and recessiveness are the outcome of natural selection acting directly in their favour, or are indirect consequences following from the nature of genetic and metabolic networks, is an issue that has been debated for long. This can be illustrated by contrasting Provine's implicit assumption (quoted above), that dominance is an evolved trait, with the following conclusion: 'Although natural selection might alter the precise activity of wild-type enzymes in particular cases, the present result lends strong support to the notion that the recessivity of mutations is a simple consequence of metabolism, as Wright suggested.' (Orr 1991). Misunderstandings have been rife in the arguments concerning the origin of dominance: for example, Orr's representation of Wright's position is not entirely accurate. What Sewall Wright (1934) in fact said was: 'It must be remembered that whatever the *evolutionary* mechanism by which a particular gene complex has been reached, the state of dominance of all of the genes in the complex must always have a completely physiological explanation [emphasis added].' Evidently, his contention was that evolution had not worked in favour of dominance *as such*. R. A. Fisher (1934), in contrast, held that 'the great excess of recessives among observed mutants was the result of many of them having been progressively modified to the recessive condition during a very long period of previous occurrence of the same mutation'.

The problem of dominance assumed pre-eminence during the early days of the neo-Darwinian synthesis, and the desire to find an evolutionary explanation for it was but natural. Four of the giants of modern evolutionary theory—Fisher, Wright, Haldane and Muller—, among others, contributed to the lively discussion that ensued. Fisher (1930) and Wright (1934) fairly early adopted diametrically opposite attitudes, and soon the debate turned contentious, developed confrontationist overtones, and attracted a substantial secondary literature. On going through the arguments of Fisher, Wright and their respective supporters, one tends to concur with Provine (1992) that the dispute was a reflection of the deep disagreement between the principal protagonists about details of the evolutionary process. As it often happens in such situations, the dispute kept being 'settled', first by one side and then by the other, by each to its own satisfaction.

Provine's statement suggests that, if the past is a reliable guide, we are destined to live with alternative and (supposedly) mutually exclusive explanations for dominance and recessiveness for some time. His prediction may be correct. But it cannot be ruled out that the approaches of both Fisher and Wright will be vindicated eventually. This point of view relies in part on the many instances in the history of biology in which disputes, or variant paradigms, were resolved neither in accordance with the hypothesis of one paradigm supplanting another by means of a scientific revolution (Kuhn 1970) nor according to Max Planck's oft-quoted assertion that new scientific theories replace old ones only after the death of all the adherents of the old theory. Instead, seemingly irreconcilable differences in biology have been settled by the coming into being of a synthetic framework that accommodates previously opposing views. The conflict between Mendelians (or geneticists) and Darwinists (or biometricians) in the beginning of this century is one example. A second example is provided by the supposed dichotomy between preformation and epigenesis, or mosaicism and regulation. These have long been propounded as rival conceptual frameworks for explaining the stereotyped patterns that emerge during embryonic development

(Wilson 1925). Formally analogous ideas have surfaced recently in terms of the 'prepattern' versus 'positional information' hypotheses (Stern 1968; Wolpert 1971), and already the signs are there that depending on the situation both points of view can be correct (Newman 1992). The reason why many disputes in biology tend to end in what might be termed peaceful coexistence is, of course, that natural selection is opportunistic and has solved the same problem in more than one way.

2. Levels of analysis

One can attempt a molecular analysis of dominance in terms of the properties of primary gene products, protein subunit interactions and so on. Such an approach makes sense if the relevant trait is directly related to a DNA sequence or transcript or to protein structure (Hodgkin 1993). But the approach can lead one astray if the trait depends on the activity of an enzyme situated downstream in a long chain involving other enzymes. Or, the trait in question may be many steps removed from primary gene activity, and dominance at the level of a trait need not be correlated with the corresponding property at the level of the gene. Xeroderma pigmentosum in humans is due to a recessive gene if one concentrates on the cancer and premature deaths that it leads to; on the other hand the same gene is dominant if one is interested in a harmless effect due to it, namely facial freckling (Stern 1960). When a trait is multigenic in origin, whether the wild type is dominant or recessive to a mutation can depend on the genetic background. For example, among the genes involved in the pathway regulating alkaline phosphatase activity in *Neurospora crassa*, $preg^c$ is normally fully recessive to $preg^+$ when it is in a $nuc\text{-}1^+$ background, but becomes dominant to it in a $nuc\text{-}1^c$ background (Metzenberg and Chia 1979). In terms of the implications for dominance and recessiveness, there is a qualitatively different aspect to the working of a gene that encodes an enzyme (or, in general, a catalyst), of a gene that encodes a structural protein, and of a noncoding but otherwise functional sequence of DNA: in short, the issue is fraught with subtleties. At the same time, metabolic regulation and enzyme reactions are relatively well-understood areas and a great many genetic variants exert their effects by influencing levels of enzyme activity. For these reasons, unless stated otherwise it is implicity assumed in this essay that phenotypic traits of interest are dependent on enzyme-catalysed reactions (the Discussion attempts to redress this lack of balance). Secondly, the relevant literature contains vastly more articles from the evolutionary point of view than those that provide arguments based on physiology. Also, one can draw lessons from evolutionary arguments even when they are wrong. Accordingly, much of what follows presents the views of Fisher, Haldane and Muller. This is not meant to suggest that Wright's approach to the problem of dominance and recessiveness downplayed the importance of natural selection; rather, he held that selection, if present, played an indirect role.

As with any other aspect of the phenotype, dominance and recessiveness must have appeared on the scene, so to say, during the course of evolution. If this was an automatic consequence of organismal physiology, rather than being the result of a specific selective process, a crucial parameter would have been the level of complexity of regulatory and metabolic networks. With an increase in the level of complexity one would expect, on the whole, a decrease in the strength of influence of any single gene on a given aspect of the phenotype. Conversely—in the simplest situation—one would expect the contribution to organismal phenotype of DNA or a primary gene

product to be equal from each functional allele. The observation would then be of codominance (as seen with the A and B blood-group antigens, for example).

3. Evolutionary models

Fisher (1930) asserted that most mutations are likely to be (a) maladaptive and (b) selected against, both in the heterozygote and in the homozygote. This implies that when the mutation first occurs, it is at least partly dominant over the wild type *at the level of fitness*. Note the distinction between dominance at the level of a trait (Mendel) and dominance at the level of fitness (Fisher). Adverse selection against the mutant allele will be countered by recurrent mutation and will result in a state of balance. Fisher's theory is that if an unfavourable gene is continuously produced by mutation, selection will favour genes—modifiers—that ameliorate its phenotypic effect. The modifier gene is assumed to make no contribution to fitness other than by modulating the mutant gene's effects. For all practical purposes the unfavourable allele is present only in the heterozygous state when it first arises, so it is the heterozygote that is principally subject to modification. It follows that the fraction of the population exposed to selection in any generation is very small (being limited by the mutation rate), and so the process of dominance modification is extremely slow.

Why might selection act in favour of dominance of the wild type? Fisher noted that dominance and recessiveness are not advantageous by themselves. Rather, dominance evolves because a heterozygote that resembles the wild-type homozygote is more fit than one that does not. What about those mutations that are dominant (and not recessive) to the wild type? Fisher's contention was that dominant mutations known to us have very strong effects on the phenotype. They are on the whole likely to be more harmful than comparable recessive mutants. Therefore, dominant mutants are exposed to strong adverse selection as soon as they arise and there will be little opportunity for them to evolve to recessiveness.

Fisher's model attracted much criticism, most of it on the ground that it entirely ignored possible genetic or physiological bases for dominance. Wright (1934) drew attention to two points. Firstly, according to the model the rate of evolution was determined by the rate at which dominance modification became necessary—basically, the mutation rate at which an unfavourable allele appeared. The rate of evolution would be so low as to be swamped by any selective effects of alleles at the modifier locus: Wright held it to be unlikely that the modifier was exactly neutral. Secondly, the process, being mutation-driven, was inherently unreliable in small populations and could be overwhelmed by drift. With an adverse selection coefficient of 0·8 against the mutant homozygote, recurrent mutation occurring at a frequency of 2×10^{-5}, and an initial frequency of a modifier allele of 0·1, the simplest model shows that it takes about 50,000 generations for over 90% of the heterozygotes to exhibit dominance (Sved and Mayo 1970); even this is true only for an infinite population. To quote Wright (1929): '... if mutation rate is of the order of one in a million per locus, an interbreeding group of less than a million can show little effect of selection of the type which Dr. Fisher postulates....'

Haldane (1930) offered a different criticism of Fisher's theory. His reasoning was based on the argument that a single copy of the modifier could not be advantageous in a wild-type homozygous background; if it was, it would spread independently of the modifier effect. Rather (ignoring the possibility of strict neutrality), Haldane

assumed that on its own the modifier was likely to be mildly deleterious. Typically, he went on to make a numerical estimate of the consequences. He assumed that the modifier was subject to a small but significant adverse selection coefficient k', say lying between 0 and 0·01. According to Fisher the beneficial effect of modification acted on the heterozygote; Haldane assumed that this corresponded to a selective advantage k relative to the mutant homozygote. Now he used the result that in polymorphisms maintained by mutation–selection balance, the heterozygote comprises a fraction $2\mu/k$ of the population (Fisher 1930), where μ is the mutation rate. Therefore, in order for modification to evolve, k' must be smaller that k times $2\mu/k$, or smaller than 2μ. With a mutation rate of 1 in 10^6, this implies that k' must be smaller than 2×10^{-6}. However, by assumption k' can have *any* positive value less than 0·01. Haldane's conclusion was that the odds were over 5000 to 1 (0·01 divided by 2×10^{-6}) against any particular modifier being selected as a result of the Fisher effect.

Accepting the basic premise that dominance *was* an evolved trait, Haldane (1930) went on to offer his own alternative for how it could have evolved. He suggested that Fisher's modifiers were none other than super-active variants of the prevailing wild type, selected precisely because they were as good in one dose as in two (implicitly assuming that the mutant form was a null allele). Modification would thereby offer a margin of safety by buffering the heterozygote against possible deleterious effects of a reduction in gene activity. Haldane (1956) returned to the problem much later and put forward another mechanism for the evolution of dominance. This time the reason for invoking evolution at all was identical to the one used by Fisher (1930): the wild type must have arisen as a rare mutant many times in the past, and in past environments *it* was likely to have been recessive to the then-prevailing wild type. Because existing wild-type alleles are dominant to most mutant alleles, the state of dominance must have evolved concomitantly with selection in favour of the allele. In adopting this line of reasoning Haldane drew on his analysis of the spread of industrial melanism in lepidopterans. There the melanic form is dominant, and he thought it likely that dominance had co-evolved with the melanic trait. A heterozygote in which the melanic form was dominant would have its fitness raised to a level corresponding to that of a homozygous melanic moth. In contrast to the model of Fisher, Haldane's allows for modification to act on a substantial proportion of the population (the heterozygotes not being maintained by mutation–selection balance) and therefore to spread more rapidly.

Muller (1950) made a searching examination of the problem of dominance in conjunction with the formally similar phenomenon of dosage compensation. Dosage compensation refers to the functional equivalence, at the phenotypic level, of different copy numbers of sex-linked genes in males and females. Muller had shown that dosage compensation worked not just with mutant alleles but also with their normal counterparts. Normal males can be considered to be effectively heterozygous in respect of any sex-linked gene in the sense that they have one wild-type allele and the other missing, the latter being equivalent to a null allele. The observation is that the 'heterozygous' male is, in respect of a compensated gene, equivalent to the homozygous female: thus the single wild-type allele in the male is dominant over the absent-allele condition. (Curiously, a dosage effect, rather than dosage compensation, appears to hold when the female is the heterogametic sex.) Two points made by Muller are of interest in the present context. Firstly, evolution advances by the incorporation of

genes that, when taken singly, have imperceptibly small effects. Secondly, dosage compensation leads to a remarkable reduction in potential phenotypic differences between the sexes, indicating that it is the result of an evolutionary process. This suggests that dominance too could have evolved, possibly by an analogous mechanism. It could have done so through the incorporation of 'mutations which cause certain specific types of nicely adjusted gene interaction, favourable for survival, and not having this survival value too much obscured by pleiotropic effects' (Muller 1932).

Muller differed from Fisher and Haldane in saying that modifier genes that tended to make the heterozygote resemble the wild-type homozygote would evolve not so much because they raised the fitness of the heterozygote, but because they provided a 'margin of stability' to the organism and insured it against both environmental and genetic effects of varied origin. The reasoning goes like this. Suppose the gene in question codes for an enzyme. Other things being equal, the rate of the reaction catalysed by the enzyme will increase with the enzyme's activity and eventually appear to reach a plateau. Clearly, the less the enzyme made, the lower the rate and the more significant the effect of any influence tending to perturb enzyme level. Therefore, according to Muller, selection will favour modifiers that push the reaction well into the region of saturation as a function of enzyme concentration (more precisely, activity). In other words, selection will cause the substrate concentration to become rate-limiting. That accomplished, one functional allele less or more makes no difference, implying that the wild type is dominant to all mutants that result in reduced activity—or, of course, enhanced activity. Plunkett (1932) independently put forward a theory similar to Muller's and suggested that dominance could arise via buffering of the organism against phenocopies produced by environmental variation.

Forsdyke (1993a, b), while acknowledging that both dominance and dosage compensation create a margin of safety within which cellular metabolism can function, suggests a novel basis for the action of selection. His starting point is the observation that when a cell is invaded by a pathogen, or subject to environmental stress, it scales down production of a majority of its proteins and embarks on synthesis of a subset of novel proteins (the heat-shock proteins). The reason for this, according to Forsdyke, is that the pathogen begins to make large quantities of its own proteins. Were the cell to continue with an unchanged rate of self-protein synthesis, the total cellular protein concentration would rise to unacceptably high levels and would lead to a defensive response on the part of the cell leading to degradation of 'self' (as well as 'non-self') proteins. This 'sudden general fall in the concentration of normal proteins... would severely compromise cell function if there were not a margin of safety.... Thus the heat-shock response would constitute a powerful evolutionary force acting on wild-type homozygotes.' Arguing along similar lines, he concludes that the heat-shock response 'would have created a much greater selection force for the evolution of a margin of safety in males', i.e. in the heterogametic sex. What about birds and butterflies, animals in which the female is the heterogametic sex? Forsdyke's prediction is that here too dosage compensation will be found to operate at the level of protein concentrations, even if not at the the level of enzyme activities.

4. Physiological models

The basic idea is that effects on the phenotype are often many steps removed from any primary gene product. If not, as mentioned earlier, functional alleles would be

expected to be codominant (Wright 1934). Also, with most genes having pleiotropic effects—elsewhere, Wright (1964) uses the phrase 'almost universal pleiotropy'—, not only do single genes influence more than one aspect of the phenotype, but many genetic loci influence any single aspect. It is then plausible that the normal physiology of the organism is not affected by small changes in the level of activity of any *one* gene. As we have seen, the same result is expected when the phenotype is based on a reaction catalysed by a single enzyme and the activity of the enzyme is high enough. Kacser and Burns (1981) developed a detailed scheme that lent support to Wright's hypothesis but went beyond it. Specifically, suppose n enzymes with activities proportional to $E_1, E_2, \ldots, E_n$ sequentially catalyse the conversion of a substrate to a product via n intermediates. It can be shown that at substrate levels that are far lower than the K_ms of the enzymes that act on them, and when the concentrations of the initial and final metabolites are held fixed, the steady-state flux through the pathway is given by an expression of the form

$$F = \frac{C}{(1/E_1 + 1/E_2 + \cdots + 1/E_n)}.$$

The sensitivity of the flux to the reaction catalysed by the ith step, Z_i, is defined as the proportional change in flux relative to a given proportional change in the activity of the ith enzyme:

$$Z_i = \frac{\partial \ln F}{\partial \ln E_i}.$$

From this it is not difficult to derive the result that Z_i can be written in the form

$$\frac{1/E_i}{(1/E_1 + 1/E_2 + \cdots + 1/E_n)}.$$

If n is large, and the various E_is are comparable, it can be shown that Z_i is of order $1/n$, or in other words very small. The implication is that over a wide range of enzyme activities the flux is essentially insensitive to the level of any *particular* enzyme. To the extent that the trait of interest is a reflection of the flux, that trait will be the same, irrespective of whether an individual has one or two copies of some gene. Therefore an allele that confers lowered, or even zero, activity is recessive to the wild type. As we have seen, both Muller and Wright had argued that the margin of safety inherent in enzyme-catalysed reactions applied even to single reactions catalysed by one enzyme. The interesting aspect of the Kacser–Burns result is that each reaction in a pathway may be enzyme-limited but the flux at steady state is not. This is true so long as substrate concentrations are low and the pathway has many members. 'Safety in numbers' is the explanation for the 'margin of safety'.

In the Kacser–Burns result the assumption that all enzymes function at substrate levels well below saturation is an important one: strictly speaking, dominance is not inevitable (Cornish-Bowden 1987). This means that either as a result of natural selection, or for other reasons, metabolic pathways must be so shaped that substrate levels are well below the K_ms of their respective enzymes. To put it differently, the relevant enzymes need to be capable of functioning at high velocities relative to the flux they support if non-functional alleles are to be recessive to the wild type.

5. The evidence

Let us examine the evidence as it pertains to the following four questions: (i) Can the degree of dominance be modified by selection? (ii) If yes, can such a process be accommodated within what we think are plausible values for mutation rates, selection coefficients and population sizes? (iii) Will a purely physiological explanation for dominance suffice in the context of what we know about intergenic interactions (in general) and metabolic pathways (in particular)? (If the answer to this question is yes, the role of natural selection in the evolution of dominance is moot.) (iv) Are there data arguing against either an evolutionary or a physiological model?

Before proceeding, two comments are in order. As already stated, whatever explanations we consider apply only to cases in which it is the wild type that is dominant. (We have noted that the closer an observed phenotype is to some property of a primary gene product, the more likely it is that different functional alleles are *co*dominant). Fully dominant mutations, meaning situations in which the wild type is recessive, are known of course. Albeit a small minority of all mutations, their existence will need to be accounted for. A purely physiological explanation may suffice in their case. Alternatively, as Fisher argued, dominant mutations are a priori likely to be extremely harmful when compared to recessive mutations; and, in conjunction with their being expressed in heterozygotes, are unlikely to exist long enough to evolve to a recessive condition. The other comment is that, in discussions concerning a possible evolutionary basis for dominance and recessiveness, there is some confusion regarding exactly what category of genes is being discussed. On the one hand, there is the dominance of the wild type to recurrently occurring mutations that are likely to be harmful. In contrast, a newly arisen advantageous mutation can supplant the existing wild type and, in the course of its passage to (near-) fixation, can become dominant to the same set of harmful mutations as well as to the previous wild-type allele. This was Haldane's explanation for the observed dominance of the melanic form in lepidopterans. The situation to which most theories apply is, however, the first, meaning the dominance of the prevailing wild type over recurrent mutations that are not likely to have been wild-type alleles in the past.

Dominance modifiers exist and selection can act on modifiers in the desired direction (see Sved and Mayo (1970) for references). To cite one example, Ohh and Sheldon (1970), working with the mutation *hairy wing* in *Drosophila melanogaster*, showed that selection was successful in changing the mean bristle number on and near the second longitudinal wing vein from 16·13 in *Hw/Hw* flies at the beginning of selection to about 6·5 at the end (the homozygous wild type does not have any of these 'extra' bristles). The mean bristle number in *Hw/+* flies was 4·71, and in *Hw/Y* flies 6·32; these did not change significantly during the experiment. Here, selection acted on the homozygote and led to near-dominance of *Hw* at the original level of the heterozygote. In other experiments it was shown that selection could act equally well on the heterozygote and raise it to the level of the *Hw/Hw* homozygote. Experimental demonstration of the evolution of dominance by artificial selection is relevant to the situation in the wild, because it shows that genes capable of modifying dominance are not uncommon (Sheppard and Ford 1966). The phenomenon of genetic imprinting is yet another evidence that modifier loci exist. Studies of imprinting show that an allele can be active or inactive depending on whether it comes from the male or the female parent. This property can be under the genetic control of other loci, and the latter

are formally analogous to the dominance modifiers postulated by Fisher (Sapienza 1989). Models for the evolution of imprinting (Chandra and Nanjundiah 1990) make it plausible that selection can act in favour of genes capable of modifying dominance.

As regards the second question—whether selection pressures of the order of the mutation rate can be effective for causing evolutionary change—, the point remains unsettled. It is tied up with, among other things, the size of the interbreeding population within which dominance is supposed to evolve and the probability of the process being swamped by migration from other populations, not to mention a reasonable estimate of the time available. We need much more data from the wild than we have presently before the issue can be properly addressed.

The present consensus is that the third question must be answered yes in the light of the analyses of Wright and Kacser and Burns, at least in so far as enzyme-mediated metabolic pathways are concerned. The Kacser–Burns model assumes that most substrates occur at levels far below the K_ms of their corresponding enzymes (or that the enzymes work well below saturation). Kacser (1987) has argued that, on grounds of chance alone, it is unlikely that most of the enzymes in a pathway will operate at substrate levels close to or above the corresponding K_ms. As to why substrate levels tend to be smaller than the respective K_ms, the explanation may have to do with thermodynamic efficiency and the reasons for reversibility or irreversibility of specific enzymes (Gautan 1988). Another purely physiological explanation for dominance is based on the existence of DNA sequences that can bind proteins encoded by particular genes. It can be shown that because of this the cell interior is buffered with respect to variations in the numbers of copies of those genes. Such buffering can explain both dominance of the wild type and dosage compensation (Chandra and Nanjundiah 1993).

The likely outcome of physiology is not always as clear. A number of findings from recent studies of *Drosophila* development highlight a feature that is relevant for an understanding of the genetic basis of dominance. These relate to mutations in two or more genes that, taken singly, are recessive to the wild type but in combination—that is, as double heterozygotes—show a phenotypic effect (Campos-Ortega 1990). The implication is that the genes interact functionally; but even more so, that their interaction is dose-dependent. It appears that the normal phenotype is based on a fine balance being achieved between the levels of gene products encoded by the various loci, and this accounts for the phenotypic effect in double heterozygotes. A similar explanation has been put forward for the observed dominance relationships among the alkaline phosphatase pathway genes of *Neurospora crassa* (Metzenberg and Chia 1979). In such cases the recessiveness of single gene mutations cannot be 'automatic' consequences of the physiology. On the contrary, the observation that single mutations are recessive but double heterozygotes show a phenotypic effect would argue in favour of a selectionist explanation. The occurrence of double mutations being extremely rare under natural conditions, selection against them would not be expected to lead to significant evolutionary consequences.

The last question is in some respects the most relevant. The conventional categorization of a gene as recessive or dominant has nothing to do with its effect on fitness, either in the heterozygote or in the homozygote. On the other hand it is precisely fitness-related consequences that are relevant for evolution. It is a fact that, when measured in heterozygotes, most so-called recessive mutations, in particular recessive lethals, show clearly discernible detrimental effects on fitness. This is true

in a number of species. Such mutations are more appropriately called dominant lethals with low penetrance (Stern 1960). Given this situation one may well wonder why the supposed margin of safety built into the physiology of metabolic networks does not operate in those four to five per cent of the heterozygotes for a 'recessive' lethal that die. In *Drosophila*, the heterozygous effects of mutations affecting viability are more marked in the case of mildly deleterious mutants than in the case of those that are lethal when homozygous (Charlesworth 1979). In other words there is, counter-intuitively, a negative correlation between how harmful an allele is when homozygous and how dominant it is when in heterozygous combination with the wild type. On both the Fisher and the Haldane models the correlation is nil, but we do not know whether other models might account for it. One can argue that the more deleterious a variant trait in terms of individual fitness, the more important it would be for the organism to evolve dominance of the wild type with respect to that trait. But the calculations do not indicate that dominance evolves at different rates for genes with drastic effects and genes with minor effects.

This seemingly paradoxical negative correlation is actually expected on the basis of physiological models. As we have seen, the theories of both Wright and Kascer and Burns depend on the familiar law of diminishing returns relating the rate of reaction catalysed by an enzyme to the enzyme's activity. It is straightforward to demonstrate that, as a consequence of this law, the less active an allele, the closer the heterozygote is to the wild type when measured relative to the difference between the two homozygotes. This means that the wild type allele will exhibit a more pronounced dominance when in combination with a completely inactive allele than with a partially active allele (the latter assumed to be only slightly deleterious when homozygous).

Following Kacser and Burns (1981), Orr (1991) has adduced what, on the face of it, looks like a serious objection to all evolutionary theories of dominance that require a central role to be played by selection acting on heterozygotes. Basically, the objection is that the wild type is dominant to most mutations even when the normal condition of existence of the organism is haploid. In his list of 52 mutations in the alga *Chlamydomonas reinhardtii*, not a single one is dominant (Orr 1991; table 1). The point is that *C. reinhardtii* is said to spend the overwhelming proportion of its time as a haploid (the observations in table 1 were carried out on temporary dikaryons

Table 1. Dominance of mutations in *Chlamydomonas* and *Drosophila*.

	Dominant	Semidominant	Recessive
All *Chlamydomonas* mutations	0	7	52
Chlamydomonas flagellar mutations	0	1	24
Drosophila mutations	0	13	208

Taken from Orr (1991). 'Semidominant' means that the heterozygote resembles the wild-type homozygote to a large extent but is not identical to it. On first sight it would appear that the pattern in man is exactly the opposite: the latest edition of the McKusick catalogue (1992) lists 2470 autosomal dominants and 671 autosomal recessives (fully validated cases). But, as McKusick discusses, this imbalance stems from many causes. His conclusion is that 'most "visible" mutations—i.e. those that cause phenotype changes that are evident to the unaided senses—are recessive'.

or rare vegetative diploids). If true, it would seem to argue strongly against the possibility of dominance evolving via selection on heterozygotes because there *are* no heterozygotes to speak of. More to the point, many traits that exhibit dominance, such as presence of a flagellum, are haploid-limited: normally they are not expressed at all in diploids. Note that this creates difficulties not just for theories demanding selection in favour of modifier genes, but also for any postulated process involving the buffering of the heterozygote against variable environments and varying genetic backgrounds.

6. Conclusion

Other things being equal, a purely physiological explanation for dominance is to be preferred over an explanation requiring the evolution of dominance by natural selection—if for no other reason because it requires fewer assumptions. Dominance can then be included among those biological phenomena that arise as an offshoot of nonspecific developmental controls, without needing the mediation of natural selection. However, before making this a general conclusion, some caveats are necessary. Firstly, even if metabolic pathways are the subject of consideration, the Kacser–Burns model (1981) requires further exploration, especially with regard to the roles of (a) non-Michaelis-Menten enzyme kinetics and (b) feedbacks. Secondly, one needs to know to what extent the assumption that most enzyme-catalysed reactions work at low substrate levels is justified. For, if the assumption does not hold good, or if what is important is not the stability of the flux through a pathway but instead the absolute level of a product, there need be no dominance of the wild type (Cornish-Bowden 1987).

The recent attention being directed at 'redundant' genes (Manjrekar 1993; Thomas 1993) has an interesting bearing on the problem of dominance. (Quotation marks have been used in the previous sentence in order to point out that the usage is erroneous but becoming accepted: if some copies of any gene are really in surplus, one ought to expect a functional degeneration of all but one of the copies (Haldane 1933), and indeed this has been found in studies on tetraploid species of fish (Allendorf 1978).) The specific observation is that the absence of one or the other of these genes does not result in any obvious phenotypic defect. In this sense, whenever any loss-of-function mutation is recessive to the wild type, one of the two wild-type alleles can be said to be 'redundant'. Alternating bouts of positive and negative selection have been suggested in order to account for the presence of cryptic, meaning normally 'redundant', genes in microbes (Hall *et al.* 1983). Perhaps we need to think along similar lines if we want to understand the existence of 'redundant' genes in higher organisms.

Especially in the light of Orr's seemingly definitive settlement of the problem, it is necessary to investigate whether episodic selection for dominance modification in diploids can work when the population consists of haploid individuals most of the time. If episodic selection can be shown to be an implausible explanation, can the action of natural selection be ruled out in a situation such as that of *Chlamydomonas*? No, as a simple example shows. Consider a modifier locus at which one allele can act as a dosage-dependent positive regulator of an essential gene *G* at the locus of interest. Linkage disequilibrium will arise between the two loci and essentially all

mutant alleles of G as well as the wild-type allele will be found within a genetic background containing the same modifier allele. Heterozygotes at G will contain two doses of the modifier, and it is conceivable that this would suffice to mask whatever phenotypic effects the mutation might have caused. Occurrence of linkage disequilibrium is not essential for the argument. Suppose there are two alleles at the modifier locus, M and m, each present at a frequency of 0·5 in the haploid state, with M being a positive regulator of the wild-type allele at G. A simple calculation shows that approximately 75% of all G^-/G^+ heterozygotes will have at least one copy of M and so will tend to resemble the wild type. To round off this point, let us recollect that microorganisms, which exist for many generations in a haploid state, and higher eukaryotes—which are essentially always diploid—have had radically different evolutionary histories. The mere fact that they exhibit similar properties (in this case, dominance of wild-type alleles) cannot be taken as evidence that the similarity points to common origins for the two sets of properties.

Dominance and recessiveness also serve to illustrate the reliability of development. If selection favours an optimal phenotype, it is to be expected that the physiology of the organism will be buffered against genotypic as well as environmental variations. This will ensure that development almost always leads to the appearance of the optimal phenotype, which becomes the modal phenotype or the wild type (C. H. Waddington (1957) coined the term 'canalization' to describe this phenomenon). A parenthetical remark: dominance of the wild type need not evolve as a passive by-product of selection for modifier genes that cause canalization. The experiments of Ohh and Sheldon (1970) showed this: they were successful in selecting for dominance of *hairy wing* over its wild-type counterpart, but the selected genotypes were not canalized and continued to exhibit a high degree of phenotypic variability. The absence of canalization may have been due to an inherent developmental instability of the mutant genotype and may not have been found if selection had operated in reverse, that is to ensure the dominance of the wild type over *hairy wing*.

In light of of the foregoing, a conservative inference would be that the recessiveness of most mutations is a consequence of both physiology and evolution, with the relative importance of the two varying from situation to situation. Unless explicitly demonstrated otherwise, it must always be presumed that, firstly, natural selection acts whenever an opportunity presents itself; and secondly, that it can discriminate between very similar phenotypes. If anything, 'redundant' genes draw our attention to what Muller (1950) described, in a different context, as the 'surpassing precision of adjustment' displayed by living organisms. Our best bet is that this precision has been moulded by natural selection, albeit in a manner not clear at the moment. It is a good idea to keep reminding oneself, especially in thinking about evolution, that absence of evidence is not the same as evidence of absence.

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