The Mutation Component of Genetic Damage

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Summary. The mutation component, M, is a measure of the proportion of the impact of a genetic condition that is attributable to recurrent mutation. For a trait maintained by balance between mutation and directional selection, M is approximately the broad-sense heritability; for a measured character where the mean and optimum coincide, M is about half the heritability. If the narrow-sense heritability is high, the impact changes relatively rapidly with a change in mutation rate. If the narrow-sense heritability is low, M cannot be predicted, but the change in impact following a change in mutation rate, if any, is very slow.

Assessing the impact of an increased mutation rate on human welfare has been a matter of concern ever since Muller's discovery in 1927 that the mutation rate can be increased by radiation. This concern has increased greatly with the realization that many chemicals, natural and man-made, are mutagenic. The technology for assessing environmental mutagens is now very sophisticated, but how much harm would be caused by an increased mutation rate is uncertain. In this article, we develop a concept that could help to reduce this uncertainty.

To assess the impact of mutation on human welfare, we need to know the extent to which recurrent mutation is a cause of disease, abnormality, impairment, or other human misery. We call the fraction of the impact of a disease or disability that is caused by recurrent mutation the mutation component of the condition. The mutation component is somewhat related to heritability, but since not all heritable conditions are equally responsive to the mutation rate, the concepts are not identical.

The first attempt to assess the total impact of mutation on the human population was made by Muller (*1*), who used an idea first enunciated by Haldane (*2*). Haldane showed that, for independent gene loci, the amount by which the average fitness of a population is reduced is between one and two times the mutation rate per gamete. Muller called this reduction in fitness the mutation load and regarded each extinction of a mutant gene by reduced viability or fertility as a genetic death. The Haldane-Muller concept is appealing in its simplicity and seemingly great generality, and it was used, although with some reservations, by the National Academy of Sciences Committee on Biological Effects of Atomic Radiation (*3*). The method has not found wide favor, however, mainly for two reasons. First, gene interactions upset the linearity of the relation on which the principle depends. If gene interaction is extreme—in particular, if there is a sharp threshold with truncate selection—the mutation load may be considerably less than the Haldane-Muller theory would predict (*4, 5*). Second, and more important, the harm is measured in the Haldane-Muller system by decreased Darwinian fitness alone; the mutation load is an aggregate of all gene extinctions, which are implicitly counted as equal. Yet nobody regards all forms of death and infertility as equal in their burden on society, and the composite measure of burden has been regarded by some as being too heterogeneous for any practical use.

An increase in the mutation rate leads, after equilibrium is attained, to a proportional increase in the mutation load. Our measure of mutation impact also has this property, but instead of measuring the burden in terms of reduced Darwinian fitness, we measure it in terms of human welfare. Throughout this article, we use impact (I) to stand for some appropriate measure of the burden caused by the trait under consideration. Ordinarily, this is proportional to the frequency. However, when we consider the effect of quantitative traits (for example, blood pressure), frequency does not have a sharp meaning; so in general we use the word impact.

In this article, we show that the mutation component of the impact of a genetic condition can often be assessed from knowledge of the mode of inheritance when this is simple, or from measures of heritability when the inheritance is complex.

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The Mutation Component

The mutation component of the burden of genetic disease and disability was first introduced by the second National Academy of Sciences genetics committee (*6*). Here we define the concept more explicitly.

If the impact, I, of a condition can be written

$$I = a + bu \tag{1}$$

where u is the mutation rate and a and b are constants, the mutation component, M, is $bu/(a + bu)$. M is the proportion of the impact (or incidence) that is attributable to recurrent mutation, and $a/(a + bu)$ is the proportion that is due to other causes. If the mutation rate is increased from u to $u(1 + k)$ the impact at equilibrium will be $a + bu(1 + k)$; it will have changed from I to $I(1 + Mk)$.

For example, a dominant disease caused by recurrent mutation has a mutational component of 1; its incidence at equilibrium is proportional to the mutation rate. If there are nongenetic causes of the same phenotype, the incidence attributable to these is measured by a. In this case, the constant b can be interpreted as the number of individuals affected by the mutant gene before it disappears from the population (*7*).

If the relationship between the impact and the mutation rate is linear, as in Eq. 1, then for an increment of mutation rate, Δu, the increase in impact, ΔI, is given by

$$\frac{\Delta I}{I} = M\frac{\Delta u}{u} \tag{2}$$

An alternative definition of the mutation component, applicable to small changes when the relationship is nonlinear, is

$$M = \frac{u}{I}\frac{dI}{du} = \frac{d\ln I}{d\ln u} \tag{3}$$

In analogy with the vocabulary of economics we might call M the elasticity of the response to an increase in the mutation rate (*8*).

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Assumptions and Definitions

Our methods are those of deterministic population genetics theory—usually equilibrium theory—and we use the conventional simplified models. (i) Generations are discrete and nonoverlapping, and the population is mating at random. (ii) The population is at equilibrium under selection and mutation. (iii) The impact of a trait is proportional to its effect on fitness. (iv) An increase in the mutation rate is assumed to affect all relevant loci proportionally. However, the mutation rates for different loci need not be the same. (v) Genetic and environmental effects are independent. Clearly, the human population departs from these idealized assumptions. However, we shall use them to derive formulas and then discuss the effects of departures from the assumptions later.

We set forth here the key definitions as used in this article. *Heritability in the broad sense* (h_B^2) is the proportion of the phenotypic variance in the population that is attributable to genetic differences. *Heritability in the narrow sense* (h_N^2) is the proportion of the population variance that is additively genetic; that is, the proportion of the phenotypic deviation of the parents from the population mean that is transmitted to their children. *Fitness* is the expected number of progeny of an individual (divided by two because of biparental reproduction). The parents and progeny must, of course, be counted at the same age. *Load* is the proportion by which the average population fitness is reduced by the factor under consideration. If the reduction in fitness is genetically caused, it is the *genetic load*. *Mutation load* is the proportion by which the population fitness is reduced at equilibrium by recurrent mutation. *Impact* (I) is the deleterious effect on human welfare. It is equal to the effect of the character on fitness multiplied by a quality factor to adjust for the amount of burden. *Mutation impact* is that part of the impact that is attributable to recurrent mutation. *Mutation component* (M) is the proportion of the impact that is attributable to recurrent mutation, defined by Eqs. 2 and 3. *Genetic death* is death before reproduction or failure to reproduce because of genetic impairment.

Because the impact, I, of a condition is taken to be proportional to its effect on fitness, Eqs. 2 and 3 can also be applied to the genetic load. This is a great convenience, for the theory of genetic loads has been worked out for many circumstances (*4*, *9*).

If the mutation impact and the mutation load are proportional and Eqs. 2 and 3 apply to both, in what ways do they differ? First, the mutation load is a measure of all harmful effects combined, whereas the impact is a measure of the mutation effects of individual diseases and impairments, taking into account the effect of each on human welfare. Second, the load is measured in units of fitness, which is appropriate for evolutionary discussions and gene frequency calculations, but not for human concerns; the impact is a measure of human well-being. Although much of the formalism of mutation load theory can be carried over to studies of impact, the approach is quite different. Furthermore, although the mutation load is greatly affected by dominance and epistasis, the mutation component is not.

Two different situations must be considered: (i) the trait is discrete and qualitative and (ii) the trait is quantitative. We include in the first category conditions such as diabetes, if this is defined as blood sugar higher than a specified threshold level. For a quantitative trait, an intermediate value of the quantity is usually optimum, and much of the effect of selection is to remove outliers and reduce the variance. We now consider these two situations in turn.

Qualitative Trait Maintained by Mutation-Selection Balance

Single autosomal locus. Assume that the genotypes, frequencies, and fitnesses are

Genotype	AA	Aa	aa
Frequency before selection	p^2	$2pq$	q^2
Fitness	w	$w(1 - hs)$	$w(1 - s)$

$$0 < s \leq 1,\ 0 \leq h \leq 1,\ p + q = 1$$

Mutation from A to a occurs at rate u per gene per generation. Reverse mutation is ignored.

From these definitions and the assumptions listed above, the proportion of a alleles next generation is

$$q' = \frac{w(1 - hs)pq + w(1 - s)q^2}{\bar{w}} + \frac{u[wp^2 + w(1 - hs)pq]}{\bar{w}} = \frac{w[q - hspq - sq^2]}{\bar{w}} + \frac{w[u(1 - q)(1 - hsq)]}{\bar{w}} \quad (4)$$

where

$$\bar{w} = w[1 - 2hspq - sq^2] \quad (5)$$

At equilibrium, $q' = q = \hat{q}$. For $h^2s >> u$, $\hat{q} \simeq u/hs$; for $h = 0$, $\hat{q}^2 = u/s$.

From the definition given above, the mutation load is

$$L = \frac{w - \bar{w}}{w} \quad (6)$$

where $\bar{w}$ is the equilibrium value (*4*, *9*).

When $h = 0$, the load (L) is u. For $h^2s >> u$, $L \simeq 2u$. These are the results first obtained by Haldane (*2*). When $h = 1/2$, so that the heterozygote is exactly intermediate between the two homozygotes, $L = 2u/(1 + u)$. It is easily shown that when $0 < s \leq 1$ and $0 \leq h \leq 1$, $u \leq L < 2u$. Since the mutation load, and therefore the impact, is nearly proportional to the mutation rate, the mutation component from Eq. 3 is very close to 1.

If several loci contribute to the trait under consideration, the load principle still holds, provided the loci are independent in inheritance and in their effects on fitness. The mutation component then is very close to 1, regardless of the number of loci involved or the magnitude of the effect of each mutant.

Multiple factors with epistasis. If there are multiple interacting loci the situation is more complicated. The work of Kimura (*10*) and Kimura and Maruyama (*11*) [for a review, see (*4*)] suggest that, for a deleterious trait maintained by mutation-selection balance, the mutation component is always close to 1 for a wide variety of dominant and epistatic interactions. The following argument suggests that this is true.

The terms in brackets in Eq. 4 represent the mutant allele frequency minus the alleles eliminated by selection plus the alleles produced by mutation. If there are a number of loci, not necessarily additive in their effects or independent in inheritance, we can extend Eq. 4 by writing

$$x' \simeq w[x - NL + 2\Sigma u_i(1 - q_i)]/\bar{w} = w[x - NL + 2U(1 - \bar{q})]/\bar{w} \quad (7)$$

where x is the total number of deleterious alleles per zygote ($= 2\Sigma q_i$); x' is the number in the following generation; N is the mean number of mutant alleles eliminated per genetic death (*12*); L is the mutation load, or the number of selective eliminations (genetic deaths); U is Σu_i, the total mutation rate per gamete; $\bar{q}$ is $\Sigma u_i q_i / \Sigma u_i$, the mutation-weighted average mutant gene frequency; and the term hsq has been neglected.

Noting that $1 - L = \bar{w}/w$, from Eq. 6, we obtain at equilibrium

$$L = \frac{2U(1 - \hat{\bar{q}})}{\hat{N} - \hat{x}} \approx \frac{2U}{\hat{N} - \hat{x}} \quad (8)$$

In words, the mutation load is equal to

Table 1. Some examples of varying heritabilities and mutation component.

Broad-sense heritability (h^2_B)	Narrow-sense heritability (h^2_N)	Mutation component (M)	Example
High	High	High	Rare dominant
High	Low	High	Rare recessive
High	Low	Low	Overdominant
Low	Low	Low	Environmental

twice the gametic mutation rate for all relevant loci divided by the difference between the mean number of mutants in those individuals removed by selection and the mean number before selection. This insightful equation was first given by King (*13*).

From Eq. 8, the load, and therefore the impact, is proportional to the mutation rate. Thus $I = bU$. If the mutation rate is changed from U to $U + \Delta U$, $\Delta I = b\Delta U$, and the mutation component from Eq. 2 is 1.

It is not necessary to assume that each locus involved in the trait contributes equally to the load. The basic assumption is that the input of new mutations in each generation is balanced by their loss from the population by selection. With mutation-selection balance, the mutation component is very close to 1. Note, however, that we are assuming that h and s are nonnegative; in other words, that the burden is a nondecreasing function of the number of mutant genes. This would rule out cases of heterozygote superiority (overdominance) or equivalent kinds of epistasis.

Effect of the environment. In Eq. 1 where the impact is $I = a + bu$, a represents the impact from environmental causes and bu that from genetic effects. The mutation component, $bu/(a + bu)$, is then simply the ratio of the genetic effects to the total impact. This will be true as long as the impact is a linear function of the mutation rate and is true of all the situations discussed so far, provided there is no interaction of genetic and environmental effects.

The quantity $bu/(a + bu)$ is analogous to heritability in the broad sense. The analogy is more apparent if the genetic damage is caused by a continuous trait, such as increased blood sugar. If a represents the incidence of excess blood sugar (by some suitable definition of excess) caused by environmental effects and bu represents that caused by genetic effects, the mutation component is simply the broad-sense heritability.

To make the treatment more like that conventionally used in quantitative genetics, let the measures 1 and 0 be assigned to individuals with and without the trait. Then the mean phenotypic value of the population is $a + bu$, and the variance is $(a + bu)(1 - a - bu) \simeq a + bu$ if the trait is rare. The two components of the phenotypic variance, a and bu, are associated, respectively, with environmental and genetic differences. Thus the heritability is $bu/(a + bu)$, the same as the mutation component.

Conclusion about traits maintained by mutation-selection balance. We conclude that for a rare trait at equilibrium under mutation-selection balance the mutation component is approximated by the broad-sense heritability.

It is assumed that there is no interaction of genetic and environmental causes. The conclusion is not demonstrated in general for arbitrary gene interaction and linkage, but the variety of special cases considered suggest that the conclusion is of wide applicability.

Traits with an Intermediate Optimum

Many human traits—height, weight, blood pressure, and various physiological processes—have a continuum of values with both extremes being disadvantageous. Most such traits are approximately normally distributed or can be transformed to be so.

Usually the damage caused by the trait increases only slightly for small displacements from the optimum, but becomes increasingly great as the deviation increases. Many quantitative geneticists, including all three pioneers, Wright, Fisher, and Haldane, have assumed that the amount of deleterious effect increases in proportion to the square of the deviation from the optimum.

Additive genes with no environmental effect. The quantitative treatment appropriate to this model was first developed by Kimura (*14*) and was applied to assessment of mutation load (*15*). The effects of the individual mutants need not be constant, but it is assumed that their effects are small relative to the total effect of the gene. Kimura used a quadratic optimum model of selection with continuous time. The derivation applies strictly to a single locus, but when selection is weak the results are also approximately correct for multiple additive loci. Most such instances that have been studied suggest that the quadratic model is a reasonable approximation and that selection is weak over most of the phenotypic range of the quantitative trait (*15, 16*).

For a trait determined by multiple additive genes and with no environmental variance, the equilibrium distribution is normal and the mutation load is

$$L = \Sigma\sqrt{2Kv_i} + 2[\Sigma(m_i/\sqrt{v_i})]^2 \qquad (9)$$

In this expression K is a measure of the intensity of selection as the squared deviation from the optimum increases, and the summation is over all relevant loci. The increments to the mean and variance of the distribution produced by a single generation of new mutants at the ith locus are $m_i = -u\bar{x}_i$ and $v_i = u\bar{x_i^2}$, where u is the mutation rate and x_i is the effect on the phenotypic measure of an individual mutant.

In Eq. 9, the first term is associated with the increase in variance produced by mutation, and the second is associated with a displacement of the mean. As might have been expected from our previous discussion, the second term is proportional to the mutation rate. The first term is proportional to the square root of the mutation rate. If the load component is, say, $Cu^{1/2}$ the mutation component is

$$M = \frac{u}{L}\frac{dL}{du} = \frac{1}{2} \qquad (10)$$

The mutation component for the part that is proportional to the mutation rate is, of course, 1.

We conclude that for weak selection and a quadratic optimum model the mutation component has two parts. The part that is due to the displacement of the mean from the optimum value by the asymmetry of mutation behaves like a trait under mutation-selection balance and has a mutation component of 1. The other part is due to an increase in variance brought about by mutation and has a mutation component of ½. It is easily shown that the transition from ½ to 1 is monotonic. Therefore the mutation component ranges in approximate value from ½ to 1, increasing with the amount of directional, as opposed to stabilizing, selection.

Effect of the environment. The work started by Kimura has been extended mainly by Lande (*17–19*). His model is that fitness is a Gaussian (normal) function of the character, which is equivalent to the quadratic optimum model for weak selection, and he assumed multiple additive loci and discrete generations.

He explicitly took into account linkage, nonrandom mating, and the effects of the environment. He assumed that the resulting distribution of phenotypes would be normal. Fleming (*20*) has verified that the normal approximation is reasonably stable under perturbations. Felsenstein (*21, 22*) showed a way to simplify Lande's derivation for a symmetrized model in which all loci contribute equally to the genetic variance of the character.

Lande demonstrated that for weak stabilizing selection the additive genetic variance is approximately

$$V_a = [2n_E V_m(W + V_e)]^{1/2} \quad (11)$$

where n_E is the effective number of loci involved in the character; V_m is the variance contributed per generation by mutation; W is a measure of the intensity of selection, roughly the inverse of Kimura's K; and V_e is the variance due to environmental factors. The total variance is

$$V = V_a + V_e \quad (12)$$

since the entire genetic variance is additive, and there is no covariance of genetic and environmental effects.

The variance due to mutation, V_m, is proportional to the total mutation rate, U. If all mutation rates are changed by a constant factor, V_m is changed by the same factor. The impact is proportional to the variance, since both are measured as squared deviations from the optimum, which on Lande's assumption of symmetrical mutation is the same as the mean. Mutation will increase only the genetic variance, so that $\Delta V = \Delta V_a + \Delta V_e = \Delta V_a$.

Since

$$V_a = C\sqrt{V_m}$$

where

$$C = [2n_E (W + V_e)]^{1/2}$$

$$V_m = \Sigma c_i u_i$$

then

$$\Delta V_a = C\{[\Sigma c_i u_i(1+k)]^{1/2} - (\Sigma c_i u_i)^{1/2}\}$$

$$= C\, V_m^{1/2} (\sqrt{1+k} - 1)$$

So

$$M = \frac{U}{V}\frac{\Delta V}{\Delta U} = \frac{\sqrt{1+k} - 1}{k}\frac{V_a}{V}$$

$$= \left(\frac{1}{\sqrt{1+k} + 1}\right)h^2$$

Clearly, as $k \to 0$, $M \to h^2/2$, where $h^2 = V_a/V$, the heritability. If the mutation rate doubles ($k = 1$), $M = 0.41\ h^2$. In this case there is no distinction between narrow- and broad-sense heritability since Lande's model assumes that the gene effects on the character (not on fitness) are additive.

The displacement of the mean when the mutation is not symmetrical has also been studied by Lande (*19*). As in the case of mutation-selection balance, the mutation component is roughly equal to the heritability. Lande has also shown that the proportionality to the square root of the mutation rate does not depend on the selection function being strictly quadratic.

Conclusion about traits with intermediate optimum. We conclude that, for a measured trait determined by additive genes and independent environmental effects, where the fitness (and therefore the impact) is proportional to the squared deviation from the optimum and where selection is weak, the mutation component for small changes in the mutation rate is between $^1/_2$ and 1 times the heritability. If the mean is close to the optimum, the factor is close to $^1/_2$; if the mean is far from the optimum, the factor becomes larger and approaches 1 as a limit when the selection is entirely directional.

Time Required to Reach a New Equilibrium

After a permanent change in the mutation rate there will be an asymptotic approach to the new equilibrium. The time required to approach within a certain distance of the new equilibrium depends primarily on two factors. One factor is the regularity of transmission of the trait from parent to child. If the trait is expressed every generation, as with a rare dominant disease, the approach is relatively rapid. If the trait skips generations, because it is recessive, because there is reduced penetrance, or because there is a substantial environmental factor in causing the impairment, the approach to equilibrium is slower. In some cases, such as for a rare recessive disease, the rate of approach is extremely slow.

The second factor is the severity of the condition. The more severe the condition, the more rapid is the approach to equilibrium, provided that the severity is manifest as a reduction in survival or fertility. As an extreme example, a dominant gene that causes a lethal or sterilizing effect owes its incidence entirely to mutations in the previous generation. A doubling of the mutation rate will cause a doubling of the incidence next generation.

The same considerations apply to a single-generation pulse of mutations. Whether the effect is immediate or is spread out over a large number of generations depends on the same two factors. Similar calculations for polygenic traits with loose linkage have been made by Lande, with qualitatively similar results (*19*).

Using Heritability to Assess the Mutation Component

Monogenic inheritance. Table 1 illustrates the most common situations. The conditions are assumed to be rare. From the table it is clear that, by measuring the two kinds of heritability, we obtain considerable information about the mutation component. Of course, if the genetics of the disease is well understood, it makes little sense to measure heritability; but these simple cases point the way to interpretation of more complex diseases.

The ambiguous case occurs when h_B^2 is high and h_N^2 is low. However, these cases have one important feature in common: the effect of an increased mutation rate in the first few generations is negligible. We conclude that if the narrow-sense heritability is low, there will be little effect of an increased mutation rate for a very long time, if ever.

Qualitative traits that are not monogenic. As a first approximation, we can use the relation between the mutation component and heritability to reach similar conclusions about traits in which the mode of inheritance is obscure. We summarize the conclusions as follows. (i) If the narrow-sense heritability is high (and the broad-sense heritability is high a fortiori), the trait has an equally high mutation component. A change in the mutation rate will eventually lead to a proportional increase in the impact. If the fitness effect is great, the new equilibrium will be approached rapidly; if the effect is mild, the approach is correspondingly slower. (ii) If the broad-sense heritability is high, but the narrow-sense heritability is low, the mutation component is indeterminate. However, an increase in the mutation rate will not have an effect, if indeed it has any, for a very long time. (iii) If the broad-sense heritability is low (and the narrow-sense heritability then is necessarily low), the trait is only slightly responsive to a change in the mutation rate, if at all, and the time required for any change is very long.

Quantitative polygenic trait. If the un-

derlying quantitative trait is symmetrically distributed, and if the optimum measurement is at the mean, the mutation component is approximately half the heritability of the quantitative measure. The heritability referred to in the theory is the narrow-sense heritability, but in the absence of significant dominance and epistatic variance (true of many polygenic traits) this is also the broad-sense heritability. If the narrow-sense heritability is low, this may mean that the trait is mainly environmental or, less likely, there is a large nonadditive component to the genetic variance. In either case the impact responds little to a change in mutation rate.

Traits with an intermediate optimum that have been studied in *Drosophila*, maize, and mice have all had a variance that is much larger than is produced by one generation of mutational input (*17*). This is probably true of human quantitative traits as well; the *Drosophila* traits studied all had large values of W (or small values of K), and the few human traits studied appear to be similar (*16*). If other traits are like those that have been studied, the time required for a significant change in variance from a change in mutation rate would be many generations, probably hundreds.

Estimating the time scale for the mutational impact of highly heritable traits. Qualitative traits with high heritability in both the broad and narrow sense are responsive to a change in the mutation rate within a few generations. For a dominant or partially dominant mutant the mean number of generations over which the damage persists is the reciprocal of the fitness reduction per mutant (*7*). However, the fitness effect may be very difficult to measure.

There is another approach. Heritability theory does not ordinarily take mutation into account, on the assumption that the input of mutations per generation is very small relative to the standing variance. In cases where this is not true—and these are the cases of greatest human importance, for they are the ones where the impact of a change in mutation rate is quickly felt—we can gain some information from parent-child correlations or concordances.

If parents with the trait are chosen and their children are observed, the proportion affected among their children provides a way of assessing the heritability in the narrow sense. If one parent is affected and the other normal, as is usually the case for rare traits, the heritability is twice the proportion of affected children. Alternatively, one can choose children and inquire as to the proportion that have one or more affected parents. Any difference between these two concordances indicates new mutations. The larger the proportion of new mutants, the faster is the approach to a new equilibrium following a change of mutation rate. By combining heritability measures with asymmetries in parent-child regressions, one can get an idea of both the mutation component and the time period over which the damage is expressed.

Discussion

In an attempt to have some generality we have been forced to make a number of approximations and simplifying assumptions. The discrete generation model is incorrect, of course; but experience suggests that it provides a reasonable approximation, especially near an equilibrium. The assumption of random mating is also reasonable for human populations. The assumed independence of genetic and environmental effects is more troublesome; it is quite likely that, in at least some cases, interactions are important. We have assumed that whatever causes an increase in the mutation rate affects all relevant loci proportionately. Perhaps this assumption is not so bad; it needs to be tested.

The most troublesome assumptions are the two remaining. One is that the impact of genetic damage on human welfare is proportional to its effect on fitness. If conditions remain constant, this is reasonable. What is more difficult to predict is whether in a changing environment the proportionality remains. We must remember that an environmental improvement that decreases the selective disadvantage of a condition will not in the long run reduce the load, because it leads eventually to a compensating higher mutant gene frequency.

The second assumption is that the population is at equilibrium with a balance between mutation and selection. Environmental improvements have greatly increased survival, including survival from genetic diseases. The rapidity of this change compared to the change of gene frequency means that quantitative assessments more than a few generations in the future are highly dubious.

All this means that the calculations we have been discussing are more reliable for conditions that are severe and have a high narrow-sense heritability. They are less reliable for conditions, such as rare recessives, mild diseases, or traits with a large environmental component, where any equilibrium is attained slowly relative to environmental changes. For such conditions we know that any increase in the impact from an increased mutation rate is very slow. One prediction that can be made is that diseases occurring after the reproductive period—an increasingly important individual and social problem—are not likely to increase rapidly from an increased mutation rate. Even if the disease has a very high heritability, the selection coefficient is small, so any increase will be spread over many generations.

The most important diseases from the standpoint of mutation are severe diseases with a high heritability. For those we can confidently predict a proportional and rapid rise if the mutation rate increases. Because genetic knowledge is increasing very rapdily, one policy is to base risk estimates on effects expected within five or ten generations, and hope that new knowledge will soon enable a more quantitative approach. This concentration on the near future has characterized both the BEIR (*6*) and UNSCEAR (*23*) reports.

Conclusion

We have introduced the mutation component, M, as a way of assessing how a rise in mutation rate increases the impact of genetic disease and disability. It measures the proportion of the impact that can be attributed to recurrent mutation. If a trait is maintained by a balance between mutation and directional selection, M is approximately equal to the broad-sense heritability. For a quantitative measurement where there is selection against extreme values, and the mean and optimum coincide, M is about one-half the heritability.

Because of this relation between M and heritability, it is not necessary that the Mendelian basis of the conditions be understood, the relevant information being provided by empirical correlations between relatives. If the trait has a high narrow-sense heritability and is severe in its effects on survival and fertility, a rise in mutation rate will produce a relatively rapid rise in the frequency of the trait. The rapidity of the response is proportional to the difference between the statistical regression of parent on child and that of child on parent.

If the heritability is low, the calculations are more uncertain, as is the reality of the assumptions. But making an accurate assessment is less urgent, because the increase, if any, is spread over a very long time—much longer than we customarily take into account in decisions concerning human welfare. The same is true

for measured characters with an intermediate optimum; unless data from experimental species are grossly misleading, the change in impact following a change in mutation rate would be very slow.

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12. In Eq. 4, $2hspq$ is the proportion by which the average population fitness is reduced by *Aa* heterozygotes, that is the load. Likewise, sq^2 is the load component for *aa* homozygotes. The number of mutant genes eliminated per genetic death is two in homozygotes and one in heterozygotes. Thus $2hspq + 2sq^2 = n_1l_1 + n_2l_2 = nL$, with $n = \Sigma n_jl_j/\Sigma l_j$ and $L = \Sigma l_j$; where l_j is the load component associated with the jth genotype and n_j is the number of mutants eliminated each time an individual of type j fails to survive and reproduce. This makes clear the extension from Eq. 4 to Eq. 7.
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Conflicting Objectives in Regulating the Automobile

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Summary. Federal regulation of automobile safety, emissions, and fuel economy is contradictory. Safety equipment and emissions control reduce fuel economy; reducing the size of automobiles is estimated to increase fatalities by 1400 a year and significantly increase serious injuries. These secondary impacts of regulation roughly double the estimated costs of achieving the individual goals. In formulating regulations, these contradictions must be taken into account, along with the effects on the price of the vehicle and its attractiveness to buyers.

The automobile has provided an unprecedented degree of personal freedom and mobility, but its side effects, such as air pollution, highway deaths, and a dependence on foreign oil suppliers, are undesirable. The United States has tried to regulate the social cost of these side effects through a series of major federal laws. Since the laws intrude on the interaction between buyers and manufacturers, they have all caused controversy.

More fundamentally, however, each law has been aimed at a single goal, either emission reduction, safety, or fuel efficiency, with little attention being given to the conflicts and trade-offs between goals. For example, the law to control emissions also reduces fuel efficiency by 7.5 percent, and a fuel efficiency law that has forced the building of smaller cars is estimated to reduce safety by resulting in an additional 1400 fatalities a year by 1984. Seeking to achieve each goal independently has promoted confusion, intensified the pressure on manufacturers, and imposed needless costs on consumers. In this article, I sketch the quantitative trade-offs among these three goals and then estimate the social costs of the existing regulations and of some proposed regulations.

Conflicting Social Goals

The undesirable side effects associated with use of the automobile include injury, air pollution, and depleted petroleum resources. Each is, at least in major part, an externality (an interaction that adversely affects one party, without market intermediation: for example, driving a car carelessly so as to injure pedestrians). The size of the three effects depends on the design of the vehicle as well as how it is operated and maintained. This is most evident in the case of safety, where selection of a vehicle and driver behavior are the overwhelming determinants of individual risk (*1*).

Physical conflicts among goals. The interactions of safety, emissions, and fuel economy are illustrated in Fig. 1. Increases in vehicle size and weight may affect safety. For instance, side door guard beams, the energy absorbing steering column, and other safety features have added about 200 pounds to the weight of an automobile which, while increasing safety, have lowered fuel efficiency. Larger vehicles are inherently safer in a crash since there is more space to absorb the impact and protect the vehicle's occupants. Additional size and weight, however, also increase fuel consumption.

Constructing and tuning an engine to reduce emissions lowers fuel economy, other factors being held constant (*2*). A small decrease in fuel economy results from the addition of equipment such as a catalytic converter because of added weight.

In order to achieve greater fuel economy, either weight must be reduced, thus reducing safety, or the engine must be retuned, thus increasing emissions. One minor interaction shown in Fig. 1 is the slight lowering of safety related to emissions control. Catalytic converters can set fire to dried leaves or other combustible material under a car.

Consumer preferences. Enhancing one attribute requires sacrificing the oth-

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