The Definition of Relative Fitness of Individuals With Specific Genetic Traits[1]

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INTRODUCTION

THE CONCEPT of relative biological (Darwinian) fitness or selective value, loosely defined as the fertility of one class of individuals relative to that of another, is well established in human genetics. This relative fertility has customarily been expressed as the ratio of mean numbers of children (Haldane, 1935) and this is probably the best simple comparison of natural selective values which can be made. This ratio is clearly implied in the parameter W (for relative fitness), when mathematically describing the effects of selection on the gene frequency of a particular gene, since we are expressing the relative proportion of genes in one generation which are transmitted to the following generation. Considering its importance, it is surprising that no exact, practical definition of relative fitness for use in human populations has been devised.

In a recent extensive study of Huntington's chorea (Reed and Chandler, 1958; Reed and Neel, 1959), an attempt to measure the relative fitness of individuals heterozygous for the dominant gene for Huntington's chorea revealed several important deficiencies in the usual method of estimating W. One important finding was that the normal sibs of choreics differed significantly in mean fertility from the general population so that the usual practice of comparing affected individuals with their normal sibs could not be used. This finding, therefore, challenges the validity of the common assumption that normal sibs of affected individuals are representative of the general population. This assumption does not appear to have been tested for other traits. Other realizations of possible deficiencies of sib comparisons were the consequence of the relatively high W for Huntington's chorea, around 0.8, since it was apparent that biases, such as age differences between affected and normal individuals, which were negligible when W was low, became important as W approached one. This paper is an attempt, growing out of the above-mentioned study, to define W for specific genetic traits more precisely. A new definition of relative fitness will be proposed and its calculation illustrated. These purposes seem best served by considering in turn (1) the "reference population" used in estimating W (the population whose fitness is compared with that of the trait in question) and (2) the methods of estimating W.

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THE REFERENCE POPULATION

The reference population may, of course, be any population in which one is interested. If one is specifically interested in comparing the fertility of trait-bearers with that of their normal sibs, then the normal sibs are the reference population. However, for the population genetics of specific genetic traits, such as traits determined by rare dominant genes, the reference population should (unless indicated to the contrary), be the general population itself. This is obvious, since all of the other parameters, such as frequency and rate of mutation from the normal allele to the mutant allele, are with reference to the general population. However, since data on the general population are almost never used, it is well to emphasize this fact. The basic problem, then, is how to obtain fertility data on the general population. The choice will usually be between (a) using government census data on women classified simultaneously by age and by number of children ever born or (b) utilizing small sample surveys, usually made for other purposes. In the past (b) has been followed and the normal sibs of the trait-bearers have been used as a sample of the general population. The implicit reason for choosing (b) is usually either that no adequate population data exist or that, even if they do, the possible biases in the sample are unimportant. This latter belief will always be justified when W approaches zero but, as the example for Huntington's chorea shows, it is not necessarily true when W is not low.

The only study using census data for the reference population appears to be this above-mentioned study of Huntington's chorea. U. S. Census fertility data for the state of Michigan, U. S. A., for 1940 were used, this being the year for which a retrospective statewide census of choreics was made. The number of liveborn children ever born per woman (married or unmarried), classified by 5-year age groups, was the available measure of fertility. A direct comparison, within age groups, is therefore possible for any Michigan sub-population living in 1940. Data on age-specific cumulative fertility for total women, such as were used here, are available in many countries. In the United States, for example, these data are available for the years 1910, 1940, and 1950, for the entire nation and for individual states. These data are usually obtained on a certain small fraction of women enumerated and consequently there is a small sampling error. In these Michigan data the standard error is about 0.05, about two per cent of the mean. Since the data are for females the question arises of their suitability for representing the entire population. As is discussed later, the *completed* fertility is what is desired so that we need consider only individuals who have reached some arbitrary age near the end of the reproductive period, say 45 years. The age-specific fertility differences between males and females then become negligible. It is clear that the mean number of children *ever* born per female cannot differ greatly from the corresponding mean for males in societies where the marriage rates and numbers of the two sexes are similar. Direct evidence for this approximate equality was found for the normal sibs of choreics by Reed and Neel (1959) and also for the normal sibs of individuals with neurofibromatosis, using the original data of Crowe, Schull, and Neel (1956). This latter calculation is presented below. These census data on completed fertility of females are therefore suitable for representing the entire population.

An important deficiency, for genetic purposes, of most census fertility data, is

that they are given for *surviving* women. As is discussed below, the most informative measure of fitness, taking into account both adult fertility and viability from birth to adulthood, is mean number of livebirths ever (to be) born per (liveborn) *newborn* individual, defined here as $\bar{B}_o$. The corresponding mean per woman surviving to (or near to) the end of reproduction is here called $\bar{B}_s$. $\bar{B}_o$ is not usually available. It is not available, for example, for any representative United States sub-population. In this one respect the use of normal sibs may offer an advantage over the usual census fertility data since it is possible, for traits recognizable at, or soon after birth, to estimate this quantity. However, depending on the nature of the trait, and the available census fertility data, estimates of $\bar{B}_s$ for two populations, *1* and *2*, may be usable to obtain valid estimates of the true relative fitness. It can be shown that this will be so (i.e., $\bar{B}_{1\cdot s}/\bar{B}_{2\cdot s} = \bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$) when (a) the proportions of newborn individuals in *1* and *2* surviving to the end of reproduction are equal and (b) $\bar{B}_{1\cdot s}/\bar{B}_{2\cdot s} = \bar{B}_{1\cdot d}/\bar{B}_{2\cdot d}$, where $\bar{B}_d$ is the mean fertility of individuals dying before the end of reproduction. When a trait decreases viability (a) is not true and this comparison is not valid. In general, comparison of normal sibs of affected persons with census fertility data should be valid, $\bar{B}_{1\cdot s}/\bar{B}_{2\cdot s}$ giving a good estimate of $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$. Census fertility data on deceased women are not available but Reed and Neel (1959), using the data on American white native-born women in *Cohort Fertility* (Whelpton, 1954), found that for women born in 1890 only about 10 per cent of the number of children ever born per newborn were born to women dying before age 47. Therefore, if (a) is true, but (b) is not, the maximum error is not over about 10 per cent; the actual error should be appreciably smaller. For workers in the United States *Cohort Fertility* enables one to approximate $\bar{B}_o$ for women born around 1900 or slightly earlier. (I am indebted to P. K. Whelpton, Scripps Foundation for Research in Population Problems, Miami University, Miami, Ohio, for valuable suggestions for estimating $\bar{B}_o$). This procedure, described in Reed and Neel (1959), requires making an assumption about the unknown cumulative fertility of women dying in the reproductive period. The assumption made was that the mean cumulative fertility of women dying at age x, say 30 years of age, is the same as that of women living at age x. This is obviously untrue in certain cases, such as women dying from chronic disease, but this effect may be offset by the greater mortality and fertility of the lower socio-economic groups. At any rate, as discussed above, the maximum error is about 10 per cent. An indication that the estimate obtained by this procedure is reasonable is found by comparing the estimate of 2.08 children ever born per white Michigan woman born in 1890 with the value (calculated in this paper) of 2.037 ± 0.240 for 107 normal Michigan sibs of sporadic cases of neurofibromatosis, reaching age 40 or over, or dying at any age, using the original data of Crowe, Schull, and Neel (1956). In other countries special fertility data may also be available for the estimation of $\bar{B}_o$.

When the reference population is the general population, the choice of method for approximating $\bar{B}_o$ will vary with the trait and the country. In deciding between census fertility data and normal sib fertility data, the fact that the census gives $\bar{B}_s$ instead of $\bar{B}_o$ must be weighed against three disadvantages of the sib comparison: 1) The true fertility of the normal sibs may differ from that of the general population, 2) the estimate of sib fertility will usually have a much larger standard error than that

of the census, and 3) the method of ascertainment may bias the fertility estimate of the normal sibs. Possibility 1) has already been illustrated and 2) is obvious. Perhaps the most obvious example for 3) is bias for large sibships, which, because of the small positive correlation between sibship size and fertility of normal individuals (Pearson, Lee, and Bramley-Moore, 1899; Fisher, 1935), would increase the observed fertility of the normal sibs. This correlation has not been clearly established for normal individuals in populations studied after 1900, but, as shown below, it probably exists. Krooth (1955) has devised a method to correct (partially) for this bias but, as will be shown, his method is open to other objections.

METHODS

In this section a new definition of relative fitness will be proposed and illustrated. Other definitions which have been advanced will also be considered.

What to measure

Because of the unlimited number of aspects of fertility which may be considered, and the considerable number which have already been used, agreement on *what* to measure seems necessary before the methods of using these measurements can be discussed. It is suggested here, as a self-evident fact, that livebirths and not total births (livebirths plus stillbirths), are the preferred units of fertility. A stillbirth makes no contribution to the gene pool of its generation. Census data, it may be noted, are usually in terms of livebirths.

1. Time span of fitness measurement: It is suggested that (with the exceptions discussed below) the most meaningful measure is mean number of livebirths ever (to be) born per *newborn* (liveborn) individual. This has previously been defined as $\bar{B}_o$. By expressing the measure in terms of the ultimate fertility that a newborn will, on the average, have by the end of his reproductive period, we get an overall measure of all factors affecting his ability to contribute genes to the next generation. By using number of children ever born, which in practice means studying individuals who have either (a) reached some arbitrary high age, say 40 or 50 years, or (b) have died at any age (we ask concerning each individual whether he is includable under (a) or under-(b); we do *not* ask with regard to (a) only or to (b) only since this would introduce a bias), we have complete information on his genetic performance, which is not the case if he is still in his reproductive period. This use will also eliminate bias due to age differences between the samples being compared. It is obvious that it is entirely incorrect to determine the mean fertility of a group of individuals of widely differing ages, without specifying age, and then compare this mean with that of another group, also unspecified for age. A child of age 10, for example, with zero children, would be regarded as equal in fertility to a married individual of age 50 years having no children, even though this child may have eight children when he attains the age of 50. It should be noted that for certain conditions having a late onset, there will be a bias for higher ages in propositi than in their normal sibs. This higher mean age will spuriously raise the observed fertility of affected individuals relative to the normal when incompleted fertilities are used. The use of completed fertility in estimating relative fitness was recommended by Haldane (1935) and has been practiced by a

number of workers but ignored by others. Krooth (1955), for example, does not consider it necessary to note the age of individuals whose fertility is being measured.

2. Time unit of the rate of fertility: It is not always obvious that the number of children born is in fact a *rate* of birth. If $\bar{B}_o$ is used, this is actually the number per generation, a generation being about 29 years (mean of all individuals, ignoring sex) in normal Western populations. It is obvious that if the length of generation differs between the two groups being compared, number per generation is an inexact, possibly misleading, measure of fitness. A simple way to avoid this difficulty is to express fertility in mean livebirths per newborn individual *per year*, instead of per generation. This procedure is illustrated below. It will be seen that the actual parental age distribution, not the mean generation length (= mean parental age) is involved.

3. Type of information to use in estimating relative fitness: The data one ideally wishes to have, for each group being studied, are, clearly, the complete life history of a large random sample of newborn liveborn individuals. $\bar{B}_o$ can then be calculated and, if age at the birth of each livebirth is also noted, livebirths per year can also be calculated. This type of data is approached when an exhaustive survey of all known cases of a trait is made for a given area at a given time, and information is also obtained on all sibs of these propositi. Because of secular changes in fertility, the data used should be kept homogeneous in time as much as is feasible without sacrificng too much data. Then, from all affected individuals, including propositi, in the sibships of the propositi, those liveborn persons who have completed their reproduction, either (a) by reaching some arbitrary high age or (b) by dying at any age, can be picked out. The total number of livebirths born to these individuals divided by their number is then $\bar{B}_o$. All individuals satisfying (a) or (b) are used, including those dying very young. It is clear that if one required only (a) there would be a bias for including the more viable, and probably more fertile, of the affected persons, while if only (b) were required there would be a bias for the more inviable. The same procedure can be used for the normal sibs. The use of the normal sibs as a reference population must be considered in the light of the previous discussion.

Unfortunately, data are often not from complete surveys and in this situation the possible effect of method of ascertainment on the estimate of fitness must be considered. A comprehensive examination of biases due to ascertainment would include those present in complete as well as in single (non-exhaustive) ascertainment. However, since at least 30 possible situations (combinations of: single or complete ascertainment, sporadic [both parents normal] or familial or both kinds of affected sibs, ditto for normal sibs, comparisons of affected vs. normal sibs, or normal sibs vs. general population, or affected sibs vs. general population) exist in which bias might arise, a comprehensive treatment will not be attempted. Instead, we may note that there are three principal possible biases which may operate in some of these 30 fertility comparisons, (a) the probability of ascertaining a sibship (in single ascertainment) is proportional to sibship size, s, (b) the probability that, for a dominant trait, among sibships having an affected parent, the probability of ascertaining a sibship of size s is proportional to $[1 - (1/2)^s]$, and (c) the fertility of normal sibs is altered because of having an affected parent or affected sib. Bias due to (a) or (b) requires a correlation between s and fertility. Bias (a) has already been mentioned

and the consequences of (b) have been given by Slatis (1955), namely, a bias for larger s in normal sibs than in the affected individuals. Bias (c) is illustrated by the findings of Reed and Neel (1959) in Huntington's chorea. Bias (a) occurs in single (incomplete) ascertainment but not in complete ascertainment, while (b) occurs in both single and complete ascertainment. If bias (c) exists, it will, of course, be independent of ascertainment.

Since no estimates of the magnitude of biases (a) or (b) have been made, it would seem worthwhile to estimate them. Because (a) will represent an increased bias in single ascertainment, relative to complete ascertainment, and because the calculation is simpler and more easily interpreted, this bias is estimated in the appendix. Although tedious, (b) could, in theory, also be calculated in a similar way, but in fact we need to know the frequency distribution of sibship sizes from matings of affected by normal as well as whether bias (c) is present. The calculation shows that for a mean population fertility of two children ever born, a linear regression of fertility on sibship size of +0.1 (a reasonable value), the bias in observed mean fertility due to (a) is +0.176. Bias due to (b) however, should be appreciably less than this since $[1 - (1/2)^s]$ asymptotically approaches one with increasing s, while bias in (a) depends directly on s, having no upper limit as s increases. With the variances in number of livebirths ever born usually observed, around six, 0.176 will be less than the standard error for samples of less than about 200. Without appreciable error, this bias may be neglected for these sample sizes. This neglect seems more justifiable when it is considered that, in practice, the precise manner of ascertainment is rarely known or is a mixture of several types, often single and multiple ascertainment.

Krooth (1955) devised a method to correct for bias (a) in comparing fertility of normal and dominantly affected sibs ascertained by single ascertainment. Bias (b), however, is not corrected when, as he suggests, the fertility of all affected sibs (sporadic and familial) is compared with the fertility of sporadic unaffected sibs. This bias is corrected for in his method for recessive traits. The absence of sporadic normal sibs in sibships of size one is an additional bias, as Krooth points out.

In summary, it seems fair to conclude that while biases deriving from the small correlation between sibship size and fertility exist in all calculations of relative fitness, they are less than the standard error of the mean fertility for sample sizes under about 200 and may be neglected. In more extensive data, it would probably be worthwhile to calculate the known biases and then correct the fertility estimates accordingly.

A definition of relative fitness based on mean number of livebirths ever born per newborn per year (B_y)

To eliminate the bias due to differences in the parental age distributions, discussed above, the following definition of relative fitness (W) is proposed: Let

x = age in years at last birthday. (On the average, this will be 0.5 years less than the exact chronological age but the small resulting bias appears in both numerator and denominator and should very nearly cancel out.)

N_i = original number of liveborn newborn individuals of genotype i whose completed reproduction is known.

$B_{i\cdot x}$ = number of livebirths born to the survivors of the N_i individuals during their xth year of life.

$\bar{B}_{i\cdot o}$ = mean number of livebirths ever born per newborn liveborn individual of genotype i.

$B_{i\cdot y}$ = mean number of livebirths ever born per newborn liveborn individual of genotype i per year, based on $\bar{B}_{i\cdot o}$ livebirths ever born.

$P_{i\cdot x}$ = parental age frequency distribution of the N_i individuals (the proportion of livebirths, out of $\bar{B}_{i\cdot o}$ livebirths, which is born to the survivors of these individuals at age x).

Then, from these definitions,

$$\bar{B}_{i\cdot o} = \frac{1}{N_i}\sum_x B_{i\cdot x}\,,\quad P_{i\cdot x} = \frac{B_{i\cdot x}}{\sum_x B_{i\cdot x}}\,,\quad B_{i\cdot y} = \frac{1}{N_i}\sum_x \frac{B_{i\cdot x}}{x}\,.$$

If we are estimating the fitness of population *1* relative to that of population *2*, the following definition will compare the true annual birth rates:

$$W = \frac{B_{1\cdot y}}{B_{2\cdot y}}. \tag{1}$$

From the above definitions,

$$W = \frac{N_2\sum_x \frac{B_{1\cdot x}}{x}}{N_1\sum_x \frac{B_{2\cdot x}}{x}} = \frac{\bar{B}_{1\cdot 0}\sum_x \frac{P_{1\cdot x}}{x}}{\bar{B}_{2\cdot 0}\sum_x \frac{P_{2\cdot x}}{x}}. \tag{2}$$

Since the customary definition of W, ignoring parental age distribution, is $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$, the effect of the parental age distribution is clearly seen. It should be noted that it is the actual distribution, not the mean parental age, which is important. A simple numerical example of these definitions may be given. If individuals of genotypes *1* and *2* have no deaths between births and the end of reproduction and, on the average, have three livebirths ever born, *1* having them at exact ages 20, 25, and 30 years, and *2* at 30, 35, and 40 years, then

$$B_{1\cdot y} = \sum_x \frac{B_{1\cdot x}}{x} = \frac{1}{20} + \frac{1}{25} + \frac{1}{30} = 0.123$$

$$B_{2\cdot y} = \sum_x \frac{B_{2\cdot x}}{x} = \frac{1}{30} + \frac{1}{35} + \frac{1}{40} = 0.087$$

and, from equation (1)

$$W = \frac{0.123}{0.087} = 1.41$$

instead of unity if parental age distribution is ignored. It is obvious that *1* will increase faster than *2* and, in time, would supplant *2*, even though $\bar{B}_{1\cdot r}$ equals $\bar{B}_{2\cdot o}$.

For this reason equation (1), or its equivalent (2), is proposed as the general definition of relative fitness because it compares the mean genetic contribution per year.

It is evident that if $\sum_x \frac{P_{1\cdot x}}{x} = \sum_x \frac{P_{2\cdot x}}{x}$, or more particularly, if $P_{1\cdot x} = P_{2\cdot x}$ for all x, equations (1) and (2) reduce to the usual ratio of means. If it is known, or probable, that the parental age distributions of *1* and *2* do not differ, $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$ is then correct. It should be noted, however, that for certain human genetic traits, especially those having onset in the reproductive period, there is an *a priori* expectation that the parental age distribution will be altered. Thus, in multiple polyposis of the colon the mean age at appearance of clinical symptoms is around 30 years and it is certain that some individuals affected with this disease have their reproduction terminated early. Their livebirths, then, have a lower mean parental age, and, consequently, greater genetic value, than those of the general population. For such diseases it may be necessary to use equation (1) even though a clear difference between parental age distributions cannot be demonstrated.

An example of estimating W *using* $\bar{B}_o$ *and* B_y

The data of Crowe, Schull, and Neel (1956), together with their unpublished data, on a survey in the state of Michigan of multiple neurofibromatosis, a rare dominantly inherited disease, are suitable for illustrating the estimation of W both by (1) and by $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$. The estimates obtained are of interest in themselves for two reasons. This disease appears to have the highest mutation rate for any human dominant trait (Crowe *et al.*, 1956), about 10^{-4} mutations per haploid genome per generation, as estimated both by direct and indirect (using relative fitness) methods. Crowe *et al.* used the method proposed by Krooth (1955) for calculating W and therefore it is of interest to compare their estimate for W of 0.527 with that obtained by the above methods.

The study of Crowe *et al.* was carried out in the years 1950–1953 and is, in large part, based on the sibships of patients diagnosed at University Hospital, Ann Arbor, Michigan between 1934 and 1953. The ascertainment of affected individuals is not complete for any specified area and, with seven exceptions, kindreds (groups of related individuals) were ascertained only once (single ascertainment). The probability of inclusion of a kindred in this study is therefore approximately proportional to the number of affected members living in the above time interval (as opposed to number of affected individuals in a sibship, since a kindred may be ascertained through more than one sibship). A similar probability applies to the ascertainment of sibships (Weinberg, 1913; Greenwood and Yule, 1914). As Krooth (1955) has pointed out, the probability for single, non-exhaustive ascertainment, of ascertaining either a "sporadic" sibship (parents normal) or a "familial" sibship (one parent affected) is proportional to sibship size (if ascertainment is only through the sibship and not through relatives). As is shown in the appendix, when ascertainment is of this type and the regression of individual fertility on sibship size is +0.1 (mean for males and females), the bias in the estimate of mean fertility of normal individuals is less than the standard error for sample sizes smaller than about 200. Since 59.5 (the fractional number

TABLE 1. COEFFICIENTS OF REGRESSION OF INDIVIDUAL FERTILITY (NUMBER OF LIVEBIRTHS) ON SIBSHIP SIZE OF THE INDIVIDUAL. DATA OF CROWE ET AL. (1956). ONLY INDIVIDUALS LIVING TO AGE 40 YEARS OR MORE OR DECEASED AT ANY AGE. MARITAL STATUS IGNORED

"Affected" = has multiple neurofibromatosis
"Unaffected" = normal sib of an affected person

Type of propositus of the kindred	Individual	Sex	Number	Regression	Standard error
Sporadic	Affected	Both	23	−0.123	0.141
	Unaffected	Males	46	+0.089	0.115
		Females	42	+0.398**	0.159
		Both	88	+0.222*	0.096
Familial	Affected	Both	23	+0.078	0.070
	Unaffected	Both	23	−0.174	0.205

** Significant at the 0.02 level.
* Significant at the 0.05 level.

is explained below) affected individuals and 107 normal sibs are available for estimating $\bar{B}_o$, this bias may be neglected.

Although the numbers available for the data of Crowe *et al.* are small, it is of interest to calculate these fertility regressions directly from their data because there appear to be no published data on the regression of individuals affected with a disease, or on fertility as measured by number of livebirths ever born, counting from the birth of an individual. These regressions were calculated for the same individuals used in estimating W and are given in Table 1. It was thought advisable to separate the "sporadic" normal sibs from the "familial" normal sibs because the former should be more representative of the general population. It is seen that only (a) sporadic normal females and (b) sporadic normal individuals (males plus females) have significant regressions, being $+0.398 \pm 0.159$ and $+0.222 \pm 0.096$ respectively. The latter does not differ significantly from the value of $+0.1$ used in the appendix, chosen for being nearer the results obtained by Pearson, Lee, and Bramley-Moore (1899) and Fisher (1935) from much more extensive data. Of particular note is the finding that there is no suggestion of a significant regression in affected individuals. It therefore appears that a significant regression occurs in the general population of Michigan but cannot be demonstrated among the affected individuals of this study. The numbers are too small to draw firm conclusions, but these findings seem reasonable if, as is the case for neurofibromatosis, the disease seriously interferes with fertility. (This follows from the fact that variance in number of livebirths born to affected individuals is determined by the varying effect of the disease on fertility, in addition to the effects of sibship size and "all other factors," while in the normal sibs only the latter two quantities are operating. Therefore the proportion of the total variance due to sibship size and consequently, the correlation, is smaller in affected individuals than in normals.)

In deciding which individuals to use for estimating fitness, the guiding principle was to obtain from the data as large a number as possible of affected individuals and their unaffected sibs whose completed reproductive performance was known and whose ascertainment was independent of viability and fertility. (The use of unaffected sibs

for a reference population is, of course, dependent on the demonstration that they are satisfactorily representative of the general population with regard to fitness.) It is not claimed that this latter goal is completely fulfilled but it is believed that major biases are absent. Some selection for severity of the disease probably occurred but, countering this, is the fact that about 27 per cent of the propositi were ascertained because they were seen for some entirely unrelated complaint and an additional 18 per cent were seen only because of cosmetic effects of neurofibromatosis. Also, all affected sibs of propositi meeting the above qualifications, are included, and there should be little bias among these. Sibships containing affected individuals selected only through an affected child were excluded, as were sibships with non-Michigan propositi and those with incomplete diagnostic or reproductive histories. Only individuals who, at the time of the study, were 40 or more years of age, or who had died at any age, were included. Therefore reproduction was nearly, or completely, ended. A higher minimum age for the living would be desirable but would reduce the numbers of usable individuals. Because neurofibromatosis may not be recognizable until several years after birth, a convention is necessary regarding the scoring of the apparently normal sibs in "familial" kindreds who died in infancy. Seven males and two females died under one year or "in infancy" in these kindreds. Since one parent was affected, half were counted as affected and half as normal. In the "sporadic" kindreds, since the parents and other ancestors were normal, these early deaths were counted as normal. In Table 2 the distribution of affected (sporadic plus familial) individuals and the normal sibs of sporadic affected individuals, by number of livebirths ever born to them, is given. The striking sex differences in fitness of affected individuals, noted by Crowe *et al.*, is apparent, males being less fertile than females. Since the number of affected males and affected females in the sample differ, while in the general population the numbers of males and females at birth is approximately equal, it is necessary to estimate the mean affected fertility as the unweighted mean of the values of the two sexes. This mean is 0.872 ± 0.191 livebirths ever born. The mean for normal sibs of sporadic propositi (the sexes do not differ so all individuals may be pooled) is 2.037 ± 0.240. There is therefore clear evidence that the fitness of affected individuals is less than that of these normal sibs. The conventional estimate of fitness, $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$ would be $0.872/2.037 = 0.43 \pm 0.11$. For the *living* normal sibs Table 2 also shows that $\bar{B}_s$ does not differ significantly from the mean expected if the age-specific cumulative fertility is the same as that of white females in Michigan in 1950 (U. S. Census data). This is evidence that these normal sibs of sporadic propositi are representative in their fertility of the general population and are a suitable reference population. The total number of normal sibs of affected in the "familial" kindreds, 39.5, is too small to warrant a separate distribution but it may be noted that the mean for all such sibs is 1.468 ± 0.337. This is appreciably, but not significantly, smaller than the mean for all normal sibs of sporadic affected. These two types of normal sibs are not pooled because there may be a real difference between them. It seems probable that the normal sibs of sporadic propositi, because they have normal parents, may resemble the general population in fertility more closely than the "familial" normal sibs.

TABLE 2. DISTRIBUTION OF INDIVIDUALS BY NUMBER OF LIVEBIRTHS EVER BORN. INDIVIDUALS LIVING TO AGE 40 YEARS OR MORE OR DECEASED AT ANY AGE. MARITAL STATUS IGNORED

"Living" = living at time of study, 1950–1953

Number of Livebirths Ever Born	All Affected		Normal Sibs of Sporadic Propositi					
			Males			Females		
	Males	Females	Living	Deceased	Total	Living	Deceased	Total
0	29.5*	13	9	10	19	11	10	21
1	2	3	4	0	4	6	1	7
2	2	2	15	1	16	9	0	9
3	0	4	7	2	9	3	1	4
4	0	0	2	0	2	2	0	2
5	2	1	2	0	2	2	0	2
6	0	0	1	0	1	1	0	1
7	0	1	1	0	1	1	0	1
8	0	0	0	0	0	2	0	2
9	0	0	1	0	1	1	0	1
10	0	0	1	0	1	0	0	0
11	0	0	0	0	0	0	0	0
12	0	0	0	0	0	1	0	1
N = No. of individuals	35.5*	24	43	13	56	39	12	51
No. of livebirths	16	31	105	8	113	101	4	105
$\bar{B}_o$ = Mean no. of livebirths	0.451	1.292	2.442	0.615	2.018	2.590	0.333	2.059
S.E. of mean	0.208	0.383	0.348		0.295	0.470		0.387
Expected mean no. of livebirths**	—	—	2.358	—	—	2.377	—	—

Mean no. of livebirths for individuals, ignoring sex:

All affected (mean of value for males and value for females): 0.872 ± 0.191.

All normal sibs of sporadic propositi (all individuals pooled): 2.037 ± 0.240.

* Unaffected individuals in "familial" sibships dying in "infancy" or under one year are counted as one-half affected and one-half normal.

** Expected if age-specific cumulative fertility is same as that of white women in Michigan in 1950. Data of 1950 U. S. Census.

The parental age distribution is needed for the calculation of $\sum_x \frac{B_{i \cdot x}}{x}$ and this is given in Table 3 for all the individuals of Table 2 whose parental ages are all known. Since the importance of parental age was not stressed at the time these data were collected, it was not always available, especially for normal sibs, and a correction becomes necessary. Only liveborn children from individuals all of whose ages at the births of these children were known, were used. If the number of these livebirths for a specified group of individuals is B_k and the number of livebirths from individuals all of whose parental ages are *not* known is B_u, then

$$\sum_x \frac{B_{i \cdot x}}{x} = \left(1 + \frac{B_u}{B_k}\right) \sum_x \frac{B_{k \cdot x}}{x},$$

TABLE 3. DISTRIBUTION OF PARENTAL AGES. LIVEBIRTHS TO INDIVIDUALS IN TABLE 2 WHOSE AGES AT BIRTH OF A LIVEBORN CHILD ARE ALL KNOWN. SEE TEXT FOR SYMBOLS

Age x	All Affected		Normal Sibs of Sporadic Propositi		Age x	All Affected		Normal Sibs of Sporadic Propositi	
	Males	Females	Males	Females		Males	Females	Males	Females
17	0	0	0	2	40	0	1	0	1
18	0	0	0	1	41	1	0	1	1
19	0	0	0	1	42	0	1	2	0
					43	0	0	1	0
20	0	1	1	1	44	0	1	1	0
21	1	2	0	2					
22	2	0	1	5	45	0	0	0	0
23	1	3	1	3	46	0	0	1	0
24	2	1	2	2	47	0	0	2	0
25	0	1	2	9					
26	0	1	3	0					
27	1	1	1	4	$\bar{x}$	28.43	30.31	32.92	28.08
28	2	1	4	6					
29	0	0	3	5	S.E. of $\bar{x}$	1.73	1.35	0.97	0.70
30	0	3	4	4	B_k	14	26	50	66
31	0	1	2	5					
32	1	1	1	2	B_u	2	5	63	39
33	1	2	2	2					
34	1	1	3	2					
35	0	1	1	3	$\sum \frac{B_{k \cdot x}}{x}$	0.514	0.902	1.585	2.452
36	0	0	4	1					
37	0	1	2	1					
38	0	2	3	2	$\sum \frac{B_{i \cdot x}}{x}$	0.587	1.075	3.582	3.901
39	1	0	2	1	(Estimated)				
					B_y	0.0165 (0.0307 for mean of sexes)	0.0448	0.0640 (0.0703 for mean of sexes)	0.0765

where $B_{k \cdot x}$ refers to the B_k livebirths. This is correct if the parental age distribution for B_k and B_u are the same or very nearly so. This should be true in most cases. The mean parental ages of affected individuals, 28.43 ± 1.73 years for males and 30.31 ± 1.35 years for females, do not differ significantly from the corresponding means of the normal sibs. The mean parental age for *sporadic* affected females (not given separately in the table), however, was 35.00 ± 1.48 years and does differ significantly from the mean for normal females, 28.08 ± 0.70. The values for the general population of Michigan in 1935 (Data of the U. S. Bureau of the Census: Vital Statistics—Special Reports), when many of the individuals in Table 3 were reproducing, are 31.559

years for males and 27.203 years for females. The observed mean for affected males does not differ significantly from the mean for Michigan fathers, but that for affected females does differ from the mean for Michigan mothers at the .05 level. The maternal age distribution of affected females therefore appears to differ from that of normal females and, in consequence, $B_{i\cdot y}$, not $\bar{B}_{i\cdot o}$, should be used. (If the numbers of affected individuals were larger, a better test would be a comparison of observed and expected numbers for convenient age groups.)

The values obtained from Table 3 for the mean number of livebirths ever born per newborn (liveborn) individual per year (B_y) are:

	Males	Females	Mean of males and females
All affected	0.0165	0.0448	0.0307
Normal sibs of sporadic propositi	0.0640	0.0765	0.0703

Then, by eq. (1)

$$W = \frac{B_{1\cdot y}}{B_{2\cdot y}} = \frac{0.0307}{0.0703} = 0.44,$$

denoting affected individuals as population *1* and normal sibs as *2* (the reference population). This is near the value of 0.43 obtained from $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$ but lower than the estimate of 0.53 obtained by the method of Krooth (Crowe *et al.*, 1956). Possible reasons for the difference (which is not statistically significant) between the estimate of 0.44 and that of Krooth are discussed below. Because $\bar{B}_{1\cdot o}$ is very significantly different from $\bar{B}_{2\cdot o}$ we are quite sure that $B_{1\cdot y}$ is significantly different from $B_{2\cdot y}$ and, therefore, that the resulting W is significantly different from unity. If this were not the case the standard errors of $B_{1\cdot y}$ and $B_{2\cdot y}$ could be calculated from the $\sum_x \frac{B_x}{x}$ of each of the N_i individuals, although this would be somewhat tedious. In general, significance tests should be applied to estimates of W as for any other estimated parameter. This practice, however, usually has not been followed.

The important question of what to do when the unaffected sibs can be shown to differ in fertility from the general population, as is the case for Huntington's chorea (Reed and Neel, 1959), must be considered. The first point to note is that, for traits affecting viability, it is incorrect to compare the fertility of *living* affected individuals with that of the living members of the general population because this would introduce a bias for mildly affected persons. One can either obtain an estimate of $\bar{B}_o$ for the general population from other sources or one can adopt a procedure used by Reed and Neel (1959). If $W_{a\cdot n}$ is the fitness of affected individuals relative to that of their normal sibs (in terms of $\bar{B}_o$ or B_y) and if $W_{n\cdot p}$ is the fitness of the normal sibs relative to that of the general population (in terms of $\bar{B}_s$, mean number of livebirths of living individuals, as of a given date, who have completed their reproduction), then, to a good approximation,

$$W = (W_{a\cdot n})(W_{n\cdot p}).$$

Since the mutation rate, μ, of a rare dominant trait is $f(1 - W)/2$, where f is the frequency of the trait at birth and the population is in genetic equilibrium, the indirect estimate of μ for neurofibromatosis is increased by a factor of $(1 - .44)/$

$(1 - .53) = 1.2$ when the value of 0.44 is used instead of the value found by Crowe *et al.* The value of f is only approximately known, being $3\text{–}4 \times 10^{-4}$, so that this change is unimportant. When W approaches unity, however, small differences in the estimates of W are seen to have large effects on the estimate of μ.

Other methods of estimating W

A number of other methods have been proposed, and used, for estimating relative fitness but they use less of the potentially available information about fitness and therefore, explicitly or implicitly, make more assumptions. They may be useful and even essential, depending on the data, but their use is justified only because complete reproductive information, from birth to end of reproduction, is not available. None take into consideration the parental age distribution.

1. Method of Krooth (1955): This has already been referred to at some length. The reader should see his paper for details of the method. In general, individuals are classified by the size of their own sibship and their fertilities are combined in such a way that the comparison of affected persons with their normal sibs is, in theory, unaffected by the bias from ascertainment and correlation between sibship size and fertility. However, as previously discussed, this bias should be very small for complete ascertainment, and, for samples of less than about 200, less than the standard error when ascertainment is proportional to sibship size. Krooth's method omits sibships of size one so that its efficiency in reducing bias due to ascertainment in large samples is in doubt. For large sample size a case can be made for using $B_{1\cdot y}/B_{2\cdot y}$ or $\bar{B}_{1\cdot o}/\bar{B}_{2\cdot o}$ and then subtracting the expected bias, using the method given in the appendix for estimating this bias. Krooth's method, it should be noted, is designed for sib comparison. The problems of using normal sibs for a reference population have already been considered. Also, his method does not specify the ages of the individuals being studied. The pooling of individuals too young to reproduce with persons who have partly or completely terminated their reproduction, when estimating fertility, cannot be defended. The value of the method of Krooth would appear to depend on how these objections are met.

2. Methods measuring the fitness of only part of the life cycle: These may be conveniently divided into (a) those measuring only viability from birth to adulthood (or even a smaller time span) and (b) those measuring only the fertility of adults, ignoring possible differential viability. Since the true measure of fitness requires data on both (a) and (b), the use of either alone requires the assumption that there is no selection in the other part of the life cycle. Under (a) we may list the "Relative Reproductive Span" (*RRS*, relative survival weighted by the parental age distribution of the general population), (Reed and Neel, 1955) and the ratio of frequency of affected adults to that of affected children. *RRS* was derived for the case where there is *a priori* knowledge or likelihood that the only selection operating is a simple consequence of earlier-than-normal termination of reproduction of some affected persons at an approximately known age. It is appropriate for diseases having onset during the reproductive period. It can be used, without this prior knowledge, to estimate the selective disadvantage due to this shortening of reproduction alone, the possibility of additional selection remaining to be determined. The estimation of adult fertility

only, (b), has been used by many workers. Like (a), it may be a necessary first step toward the determination of the fitness over the whole life span.

DISCUSSION

It has been stated in this paper that the definition of choice for W is that given by equation (1), where the reference population is either the general population or some representative sample of it. Other definitions are approximations to this, being determined from fewer data. It is necessary to add, however, that the possible data giving information on fitness, and the traits to be studied, are so varied that this more exact approach may be impossible or impractical in certain instances. A less comprehensive method must then be used. General rules of procedure for all contingencies are not possible but certain desiderata which any fitness study should consider can be listed:

1. The reference population is representative of the general population (defined in time and space).
2. The data are from as large a part of the life cycle (from livebirth to end of reproductive period) as possible.
3. The possible bias due to ascertainment is either small or is corrected.
4. The parental age distributions are compared and B_y used if appreciably different.
5. The data are as homogeneous in time and in age of individuals as is feasible. In particular, only completed (or nearly so) fertilities are used.

The emphasis throughout has been on the fitness of individuals, ideally as recognizable genotypes, and not on matings. Penrose (1949) has discussed the fitness of mating types and for a number of purposes this joint fitness is of value. But it seems clear that for analysis of the transmission of genes from one generation to another it is sufficient, and simpler, to follow individuals, irrespective of their matings, and note their reproductive performance. (Complications such as non-random segregation of chromosomes or mother-child incompatibility, which could alter the expected proportions of genotypes among the children of the individuals being investigated, are ignored here. If such a mechanism is known to exist allowance must be made for its effect since it will alter the proportion of genes transmitted between generations.)

The data of Crowe *et al.* (1956) on neurofibromatosis, analyzed in the present paper, provided an example (affected females) of a group whose parental age distribution differs significantly from the general population (of females), there being an excess of births to older mothers. It is interesting to note that Reed and Neel (1959) found that females (but not males) affected with Huntington's chorea similarly differed in parental age distribution. It is not immediately apparent why there should be an excess of older mothers since the progressive nature of both diseases might be expected to reduce reproduction at higher ages. In each case this finding shows that the parental age distribution should be taken into account and that either equation (1) or equation (2) should be used.

The analysis of fertility by separate sexes should be done to test whether, as is the case in neurofibromatosis, the values of $\bar{B}_{i\cdot o}$ differ significantly. If the sexes do not differ in fertility they may be pooled and classification by sex ignored. When there are differences and the numbers of males and females in the sample differ, the (unweighted) mean of the separate estimates of $\bar{B}_{i\cdot o}$ or B_y should be used, since, when

dealing with traits determined by autosomal genes, this will give an estimate of the fitness of all individuals, unbiased by the sex proportions in the sample. It is noteworthy that the difference between males and females found by Crowe *et al.* (1956) for neurofibromatosis was also noted in Huntington's chorea (Reed and Neel, 1959). A discussion of this phenomenon, which may be general for genetic traits with delayed onset, is given by these authors. Penrose (1950) has shown that among the mentally defective, females are more fertile than males.

Although the parental age distribution of affected females differed from that of the general population, W estimated from equation (1) (0.44) was very near that based on $\bar{B}_{i\cdot o}$ (0.43). This is probably a consequence of the slightly higher mean parental ages of the normal sibs, relative to the general population, decreasing their value of $\bar{B}_{i\cdot y}$ and, consequently, raising that of the affected individuals. It is likely that much larger differences between these two estimates of W, statistically significant, could be obtained in some data. In such cases the importance of using equation (1) would be more obvious.

In the long run the relative fitness of a particular group should be related to the relative rate of growth it would experience if it grew only through its own reproduction (i.e., without mutation or migration). This relationship, however, is not simple. It is interesting that Fisher's (1930) Malthusian parameter, m, the relative rate of increase (or decrease) of a population, can be estimated from B_y (mean number of livebirths ever born per newborn per year) and $\bar{B}_o$ (mean number of livebirths ever born per newborn). Counting the actual contribution per parent as *one-half* the number of livebirths, the annual contribution in births that a newborn individual will make is $B_y/2$. We may also consider the deaths *per year*, D_y, that a newborn individual I will contribute to the population. D_y is equal to $B_y/\bar{B}_o$ because I is $1/\bar{B}_o$ of a (specified) parent's progeny, which are being born at the rate B_y; therefore, I can be said to be born at the rate $B_y/\bar{B}_o$. If there are no secular changes in B_y and D_y, the individual's death rate equals his (own) birthrate. Therefore

$$m = \frac{B_y}{2} - D_y = \frac{(\bar{B}_o - 2)B_y}{2\bar{B}_o}$$

This definition of m (relative increase per year) has the expected property that m exceeds, equals, or is less than zero according as $\bar{B}_o$ exceeds, equals, or is less than two livebirths ever born per newborn. Since values of m can be calculated for the two groups being studied (assuming adequate data) the relative rates of growth can be compared. However, a definition of relative fitness is not easily obtained from m_1 and m_2 (for populations *1* and *2*) because m does not approach zero when $\bar{B}_o$ does. Also, a definition of W based on m lacks the direct significance of one based on reproductive performance.

In conclusion, the critical determination of relative fitness in man will probably never be easy. As the example presented illustrates, various compromises and approximations are required. There are a number of fairly simple procedures, however, which can improve the accuracy of the estimate and it has been the goal of this paper to describe some of them.

SUMMARY

An exact, directly applicable, definition of relative genetic fitness (W) is needed in the population genetics of specific human genetic traits, but this has not yet been formulated. Commonly used estimates of W, such as the ratio of mean fertilities of affected individuals and their normal sibs, may have two important sources of error: 1) the normal sibs may not be representative of the general population in their fertility, and 2) factors which affect fitness may be omitted. An example of 1) is known. A factor affecting W which is almost always omitted from consideration is the parental age distribution (age of individuals at the birth of their children).

A new definition of W, which takes into account parental age distribution is proposed and its calculation illustrated with data of Crowe *et al.* (1956) on multiple neurofibromatosis. It is shown that when the parental age distributions in the two populations being compared are the same, the proposed definition reduces to the usual ratio of mean numbers of children ever born. Other aspects of estimating relative fitness, including use of government census fertility data, are considered.

APPENDIX

MAGNITUDE OF THE BIAS IN OBSERVED FERTILITY OF NORMAL INDIVIDUALS ASCERTAINED IN PROPORTION TO THEIR SIBSHIP SIZE

The published studies on regression of individual fertility on sibship size of the individual are based on English landed gentry and nobility (Pearson *et al.*, 1899) and on German nobility and Danzig officials (Fisher, 1935). In each study only married persons are considered. The former study found regressions of $+0.05$ to $+0.12$ for males and $+0.04$ to $+0.22$ for females, values differing according to the source and treatment of the data. The latter, based on more varied data, yielded regressions for the total of 6727 couples of $+0.030$ for males and $+0.114$ for females. All these regressions are significant.

It is possible to estimate the bias in the estimate of mean fertility due to single ascertainment for any given value of the regression coefficient, b, of livebirths on sibship size of individuals. In single ascertainment the probability of ascertaining an individual is proportional to his sibship size. This is the situation usually prevailing when, for a given area, the proportion of individuals ascertained, out of the total available, is small. If the proportion becomes high, repeated ascertainment of the same individuals begins to occur and the bias for large sibships and, consequently this bias in observed fertility, decreases, reaching zero for complete ascertainment. It is emphasized that this calculation is for *normal* individuals in all sizes of sibships. It therefore slightly underestimates the bias in comparing normal sibs with the general population. At the same time, it probably overestimates the bias in affected persons, since, as the present data indicate, b for affected persons is probably less than for normal persons. Since the mean b for males and females in the extensive study of Fisher (1935) is about $+0.07$, it seems appropriate to use a value of $+0.1$, which does not differ significantly from the higher value calculated in the present study for the data of Crowe *et al.* If, in the general population,

θ_s = frequency of sibships of size s
B_s = mean number of livebirths ever born to individuals in sibships of size s
$\bar{B}$ = mean number of livebirths ever born

and θ_s' and $\bar{B}'$ are corresponding quantities for the sample obtained by single ascertainment as mentioned above, then

$$B_s = \bar{B} + b(s - \bar{s}_i)$$

$$\bar{B} = \frac{\sum s\theta_s B_s}{\sum s\theta_s}$$

$$\bar{B}' = \frac{\sum s\theta_s' B_s}{\sum s\theta_s'} = \frac{\sum s^2\theta_s B_s}{\sum s^2\theta_s}, \quad \text{since} \quad \theta_s' = \frac{s\theta_s}{\sum s\theta_s}.$$

The first equation is the regression of fertility of an individual on his sibship size, $\bar{s}_i$ being the mean size of sibships of *individuals* in the population, equal to $\sum s^2\theta_s / \sum s\theta_s$ (to be distinguished from $\bar{s} = \sum s\theta_s$). Reasonable values for the distribution of θ_s were obtained from the 1940 U. S. Census, equating it to the distribution of number of children ever born to married native-born white women age 45–49 years in the North Central states, omitting women having no children. Women having 10 or more children, who were 2.9 per cent of all women, are pooled in the census so it was necessary to guess at appropriate numbers of $s = 10$ and above, arbitrarily ending at 15. By assigning the reasonable value of 2.000 to $\bar{B}$, B_s can then be calculated and then $\bar{B}'$. These values and calculations are given in the appendix table. $\bar{s}_i$ is found to be

APPENDIX TABLE. DATA FOR ESTIMATING BIAS IN THE ESTIMATE OF MEAN FERTILITY WHEN THE PROBABILITY OF ASCERTAINMENT IS PROPORTIONAL TO SIBSHIP SIZE. A REGRESSION OF FERTILITY ON SIBSHIP SIZE OF +0.1 AND A MEAN POPULATION FERTILITY OF 2.000 LIVEBIRTHS EVER BORN ARE ASSUMED. SEE TEXT FOR SYMBOLS AND EXPLANATION

s	θ_s	B_s
1	.2028	1.5890
2	.2445	1.6890
3	.1831	1.7890
4	.1244	1.8890
5	.0797	1.9890
6	.0571	2.0890
7	.0347	2.1890
8	.0279	2.2890
9	.0167	2.3890
10	.0110	2.4890
11	.0074	2.5890
12	.0046	2.6890
13	.0028	2.7890
14	.0018	2.8890
15	.0014	2.9890
Σ	.9999	—

$\bar{s}_i$ = 5.1102.
$\bar{B}$ = 2.001 (calculated from these data as a check).
$\bar{B}'$ = 2.176.

5.1102 ($\bar{s}$ = 3.4254), $\bar{B}$ calculated from the second equation above, as a check, is 2.001, but $\bar{B}'$ is 2.176. There is thus a positive bias of about 0.176 in the sample estimate of the mean fertility of normal individuals. This bias is seen in perspective when it is noted that the variance in the mean number of livebirths ever born to the normal sibs of sporadic propositi in the data of Crowe *et al.*, age 40 or more or deceased at any age, is 6.1495. The sample size of these sibs having a standard error of 0.176 is 198.5. Therefore, for sample sizes less than about 200 the bias is less than the standard error and, without appreciable error, may be neglected. For large samples collected through single ascertainment it would probably be worthwhile to calculate the expected bias and subtract it from the observed mean.

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