RELATION BETWEEN HOMOZYGOUS VIABILITY AND AVERAGE DOMINANCE IN *DROSOPHILA MELANOGASTER*[1]

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DURING 1959–1962 we conducted experiments on the genetic loads revealed by Basc tests in irradiated laboratory stocks and by inbreeding of second chromosomes from wild and laboratory populations of *D. melanogaster*. Recently, access to a CDC 3100 computer has permitted an analysis of the relation between homozygous viability and average dominance in these data.

EXPERIMENTAL METHODS

The laboratory populations have been described by CHUNG (1962) and FRIEDMAN (1964). The wild populations came from six localities in two regions. Manoa, Waikiki, and Kapahulu are three suburbs of Honolulu, Hawaii, and Frank's, Kapec, and Capitol are three sites in Madison, Wisconsin. Within a region, the localities are 1–3 miles apart. Each locality was represented by a collection of about 200 females, whose descendants were maintained in 8 half-pint bottles, with mixing at each transfer. The collections included a minority of *D. simulans* which gradually were eliminated without artificial selection.

Basc tests were described by FRIEDMAN (1964). Second chromosomes were studied by the methods of CHUNG (1962), in which the last generation comes from the mating *cn* bw^D/+ ♂ × *Cy O*/+ ♀, where *Cy O* denotes Curly wings and complex inversions and the *cn* bw^D chromosome was selected for high sensitivity to the segregation-distorter (*SD*) locus (SANDLER and HIRAIZUMI 1959). The grandparental mating was *Cy O*/*S* ♂ × +/+ ♀, and various inbreeding levels were derived in the last generation by taking chromosomes identical by descent ($F = 1/2$), from the same grandmother ($F = 1/4$), from grandmothers who were sibs ($F = 1/8$), and from unrelated grandmothers ($F = 0$), the inbreeding coefficient F being based on the assumption that the second chromosome makes up one-half of the autosomal genome. In addition, an interpopulational outcross ($H = 1/2$) was made in the last generation, where H denotes the fraction of the autosomal genome that is an F_1 hybrid. This experiment was carried out as a twice-replicated balanced incomplete block design with three pairs of populations in each of five blocks, each pair involving two intrapopulational and one interpopulational sets of cultures, the different levels of inbreeding within each pair being carried out concurrently. The number of chromosomes tested per subset was about five, and levels $F = 0$ and $H = 1/2$ were cyclical permutations of the same chromosomes used for the inbreeding tests. The mating type is called

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intrapopulational, intraregional, or interregional according to whether the grandmother came from endogamous parents or was the F_1 hybrid between two localities in the same region or between different regions.

All cultures were kept at 24° to 26°C. The medium used was a standard cornmeal, molasses, yeast, agar type, sprayed with live yeast and containing 0.5% proprionic acid as a mold inhibitor.

THEORY AND MAXIMUM LIKELIHOOD ANALYSIS

A large body of evidence has demonstrated that apparently recessive genes have recognizable effects in heterozygotes. In man, this is the basis for detection of heterozygous carriers of the genes for phenylketonuria, galactosemia, and other recessive entities. In Drosophila, it has been shown that the *average* recessive lethal mutation induced by ultraviolet or radiation depresses viability in heterozygotes by 4% (MULLER 1950; STERN *et al.* 1952). Natural selection operates more efficiently on genes with large heterozygous effects, so that in populations near equilibrium the average viability depression in heterozygous carriers of a recessive lethal is about 2% (HIRAIZUMI and CROW 1960; OSHIMA 1963), and may be even less when tested against chromosomes for the same population.

At the opposite extreme of minimal homozygous impairment there is little evidence about heterozygous effects, but it is the experience of quantitative genetics that small effects behave nearly additively. DOBZHANSKY, KRIMBAS and KRIMBAS (1960) found that chromosomes of high homozygous viability are also superior in heterozygotes, but there does not seem to be any marked proportionality between heterozygous and homozygous effects. In fact, both their paper and the report of DOBZHANSKY and SPASSKY (1963) suggested that minimal heterozygous fitness is associated with chromosomes which are of intermediate homozygous subvitality. Such a curvilinear relationship is hard to study because of the correlation between counts of heterozygotes and homozygotes in the same culture, and we were, therefore, led to devise a model consistent with the above considerations and highly sensitive to curvilinearity, overdominance, and other possible complications. As in much of Drosophila population genetics, the experimental techniques force us to deal with whole chromosomes in the hope that their effects mimic single genes. This assumption is most plausible when the chromosomes under study are only partly inbred, or were derived a few generations back from a single chromosome.

Consider cultures segregating a marker phenotype, its heterozygote with a wild-type chromosome, and the wild type itself. Let the control phenotypic frequencies be p, q, r, respectively, and p/w, $q(1\text{-}hs)/w$, and $r(1\text{-}s)/w$ in a particular culture, where h is the average dominance of the homozygous selection coefficient s, and $w = 1\text{-}qhs\text{-}rs$ is the relative viability of the culture. Clearly w must be positive, while s and hs must not exceed 1 but are not otherwise restricted. We separate the cultures into two groups: *supervitals* with wild-type frequencies greater than the control ($s < 0$) and *subvitals* with wild-type frequencies less than the control ($0 < s < 1$). The boundary conditions indicated above for the relation between h and s in populations near equilibrium are that $h = .02$ for

$s = 1$, that $h = .5$ for $s = 0$, and that hs may have an intermediate maximum. These conditions are satisfied by a relation of the type

$$h = .50 - k|s|^a,$$

where k = .48 for equilibrium populations. If $a = 0$, then $h = .02$ for all values of s; if $a = .5$, then hs has a maximum value of .08 at $s = .48$; and if a is negative, there is progressive overdominance for decreasing values of s. New mutations, with $h = .04$ for $s = 1$, have $k = .46$.

This model may be applied by iterative maximum likelihood estimation of s for each culture, subject to an assumed value of a; evaluating the M. L. score $U_a = \Sigma u_a$ at the estimated value of s; and calculating the conditional variance of this score as

$$K_{aa} = \Sigma u_a{}^2 - (\Sigma u_a u_s)^2/\Sigma u_s{}^2.$$

the summation being over all the phenotypes within a culture (Table 1). Then the iteration

$$a' = a + \Sigma U_a/\Sigma K_{aa}$$

converges to the M. L. estimate $\hat{a}$, with standard error $1/\sqrt{\Sigma K_{aa}}$. This estimation procedure is given in standard texts on statistics (for example RAO 1952), and has

TABLE 1

Maximum likelihood scores for dominance of subvitals ($0 < s < 1$)

$$hs = .50s - ks^{a+1}$$
$$w = 1 - qhs - rs$$

Phenotype	Marker	Heterozygote	Homozygote
Probability	$\frac{p}{w}$	$\frac{q(1-hs)}{w}$	$\frac{r(1-s)}{w}$
observed number in culture	n_1	n_2	n_3
$u_s = \frac{\partial \ln P}{\partial s}$	$\frac{-\partial w/\partial s}{w}$	$\frac{-\partial(hs)/\partial s}{1-hs} - \frac{\partial w/\partial s}{w}$	$\frac{-1}{1-s} - \frac{\partial w/\partial s}{w}$
$u_a = \frac{\partial \ln P}{\partial a}$	$\frac{-\partial w/\partial a}{w}$	$\frac{-\partial(hs)/\partial a}{1-hs} - \frac{\partial w/\partial a}{w}$	$\frac{-\partial w/\partial a}{w}$

$$U_s = \sum_{i=1}^{3} n_i U_{si} \qquad \frac{\partial w}{\partial s} = -.50q + kq(a+1)s^a - r$$

$$U_a = \sum_{i=1}^{3} n_i u_{ai}|\hat{s} \qquad \frac{\partial(hs)}{\partial s} = .50 - k(a+1)s^a$$

$$K_{aa} = \Sigma n_i u_{ai}{}^2 - (\Sigma n_i u_{si} u_{ai})^2/K_{ss}|\hat{s} \qquad \frac{\partial w}{\partial a} = kqs^{a+1} ln_e s$$

$$K_{ss} = \Sigma n_i u_{si}{}^2$$

$$s = s_0 + U_s/K_{ss}|_a$$

$$\vdots$$

$$\hat{s}$$

been applied to many genetic segregations (MORTON 1963). If during iteration s becomes zero or equal to or greater than 1, the culture is deleted, since U_a is then indeterminate or zero. Supervital chromosomes ($s < 0$) may be analysed for expected frequencies p/w, $q(1+hS)/w$, and $r(1+S)/w$, where $w = 1 + qhS + rS$ and $S = -s$ (Table 2). These calculations are performed by a program called MAXLIKE written in Fortran IV language for the CDC 3100 computer. Goodness of fit of the model among cultures is tested by

$$\chi^2 = \Sigma(U_a^2/K_{aa}) - (\Sigma U_a)^2/\Sigma K_{aa}$$

with degrees of freedom equal to one less than the number of cultures accepted.

Cultures with the ratio of $bw^p/+$ to $Cy/+$ less than .2 were classified as segregation distortion (SD). Excluding SD cultures, the controls for the inbreeding experiments gave $p = .2229$ for Cy/bw^p, $q = .5207$ for $bw^p/+$ and $Cy/+$, and $r = .2564$ for $+/+$ (Table 3). The corresponding values for post-radiation chromosomes are $p = .2342$, $q = .5158$, $r = .2500$ (CHUNG 1962).

Since FRIEDMAN's data involve newly induced mutants, we took $k = .46$ to give $h = .04$ for the null hypothesis of $a = 0$. Estimates of p, q, and r are based on non-lethal cultures, pooling all experiments. With irradiated Basc males F_2 parameters are $p = .5332$ for $+$ ♂ and $asc/+$ ♀, $q = .2450$ for $Basc/asc$ ♀, and $r = .2218$ for $Basc$ ♂. With irradiated Canton-S males the corresponding values

TABLE 2

Maximum likelihood scores for dominance of supervitals ($s < 0$)

Set $S = |s|$
$hS = .50S - kS^{a+1}$
$w = 1 + qhS + rS$

Phenotype	Marker	Heterozygote	Homozygote
Probability	$\frac{p}{w}$	$\frac{q(1+hS)}{w}$	$\frac{r(1+S)}{w}$
u_S	$\frac{-\partial w/\partial S}{w}$	$\frac{\partial(hS)/\partial S}{1+hS} - \frac{\partial w/\partial S}{w}$	$\frac{1}{1+S} - \frac{\partial w/\partial S}{w}$
u_a	$\frac{-\partial w/\partial a}{w}$	$\frac{\partial(hS)/\partial a}{1+hS} - \frac{\partial w/\partial a}{w}$	$\frac{-\partial w/\partial a}{w}$

$$\frac{\partial w}{\partial S} = .50q - kq(a+1)S^a + r = -\frac{\partial w}{\partial s}$$

$$\frac{\partial(hS)}{\partial S} = .50 - k(a+1)S^a$$

$$\frac{\partial w}{\partial a} = -kqS^{a+1}ln_eS$$

$$\therefore U_S = -U_s$$

$$U_a|S > 0 = -U_a|s > 0$$

TABLE 3

Data for estimation of p, q, *and* r

Source	Total Counts					p	q	r
Chromosome II controls ($F = 0$)	Cy/bw^D	$Cy/+$	$bw^D/+$	$+/+$	Total			
Inbreeding experiment	13,691	15,851	16,125	15,746	61,413	.2229	.5207	.2564
Postradiation (CHUNG 1962)	6,974	7,529	7,827	7,442	29,772	.2342	.5158	.2500
X chromosome (FRIEDMAN 1964)	*asc*/+ ♀	*Basc/asc* ♀	*Basc* ♂	+ ♂	Total			
Basc radiated	114,412	103,086	92,974	109,165	419,637	.5332	.2450	.2218
Canton-S radiated	115,638	103,286	93,840	109,959	422,723	.4668	.2731	.2601
Total	230,050	206,372	186,814	219,124	842,360			

are $p = .4668$ for *Basc* ♂ and *Basc/asc* ♀, $q = .2731$ for *asc*/+ ♀, and $r = .2601$ for + ♂. Lethal chromosomes were defined as having less than 2.5% of the hemizygous irradiated chromosome.

HIRAIZUMI and CROW (1960) used a different experimental design to study heterozygous effects. Chromosomes isolated from wild populations were subjected to an intercross, *Cy*/+ × *Cy*/+, to determine homozygous effects (s) and a backcross, *cn*/+ × *cn bw*, to measure heterozygous effects (hs). In the first case let the observed numbers of *Cy*/+ and +/+ progeny be b and c, respectively, with expectations $(1\text{-}r)/(1\text{-}rs)$ and $r(1\text{-}s)/(1\text{-}rs)$, where r is the mean frequency of +/+. Then

$$s = 1 - c(1\text{-}r)/rb$$

Chromosomes are divided into subvital ($0 < s < 1$) and supervital ($s < 0$) as above.

Let the observed numbers of *cn* and +/*cn* progeny in the backcross be x and y, respectively, with expectations $p = (1\text{-}q)/(1\text{-}qhs)$ and $q(1\text{-}hs)/(1\text{-}qhs)$, where q is the mean frequency of *cn*/+. Neglecting errors of estimate in q, r, and s, the score for a is

$$U_a = \left(\frac{d \ln L}{dp}\right)\left(\frac{dp}{dh}\right)\left(\frac{dh}{da}\right)$$

$$K_{aa} = (x+y)\left(\frac{dp}{dh}\right)^2\left(\frac{dh}{da}\right)^2 / p(1\text{-}p)$$

where

$$\frac{d \ln L}{dp} = x/p - y/(1-p)$$

$$\frac{dp}{dh} = \frac{(1\text{-}q)qs}{(1\text{-}qhs)^2} = \frac{qp^2 s}{1\text{-}q}$$

$$\frac{dh}{da} = -k|s|^a \ln|s|$$

and $k = .48$ for equilibrium populations. Lethal cultures ($s = 1$) are uninformative, since $dh/da = 0$.

HIRAIZUMI and CROW did not carry out a control intercross with the wild type second chromosomes paired at random, but from Table 3 we may calculate $r = 23188/69948 = .3315$. Of the 735 chromosomes isolated, 68 were classified as lethal (no wild-type flies) and 144 as semilethal (0—16.7% wild type). The proportions of wild type in backcrosses were .5026, .4997, and .5088 for lethals, semilethals, and controls, respectively, with a weighted mean of $q = .5064$. Then

$$s = 1\text{—}2.0166\ c/b$$
$$p = .4936/(1\text{—}.5064\ hs)$$
$$dp/dh = 1.0259\ p^2 s$$

RESULTS

Under the null hypothesis that $a = 0$ both subvitals and supervitals tend to

TABLE 4

Analysis of subvital homozygous second chromosomes

Study	$a=0$ ΣU_a	ΣK_{aa}	Among cultures $(\Sigma U)^2/\Sigma K$	χ^2	df	$a=-.04$ ΣU_a	ΣK_{aa}
HIRAIZUMI	2.652	419.5	.02	131.82	94	20.544	473.4
Inbreeding experiment	—12.827	111.0	1.48	377.48	268	—12.235	119.7
Postradiation (CHUNG 1962)	— 8.166	71.8	.93	233.42	217	— 7.461	77.3
Total	—18.341	602.3	.56	742.72	579	0.848	670.4

Source	df	χ^2/σ^2
$a=0$	1	.44
Among studies	2	1.46

$\sigma^2 = 742.72/579 = 1.283$

have positive scores for a, only 4 of the 20 scores being negative. Allowing for variation among cultures, the total score is highly significant ($\chi^2 = 16.01$, $P < .001$). However, there is marked heterogeneity among sets of data which were accordingly divided into 6 blocks, separating subvitals and supervitals, second and X chromosomes, and F equal to or less than $\frac{1}{2}$.

Analysis of the first block, subvital homozygous second chromosomes, is shown in Table 4 for $a = 0$. Fit is close, with $\hat{a} = -.039 \pm .044$. Evidently viability depression at high levels of inbreeding is almost completely recessive.

Very different results are obtained at low levels of inbreeding (Table 5). Subvitality is much more nearly additive. The difference from homozygous chromosomes is highly significant, but there is no apparent heterogeneity among $F = 0$, $\frac{1}{8}$, and $\frac{1}{4}$. The maximum estimate for subvital, partially heterozygous chromosomes is

$$\hat{a} = 1.774 \pm 0.244.$$

WILLS (1966) obtained rather similar results with homozygous chromosomes, whereas the data of DOBZHANSKY and SPASSKY (1966) agree more closely with our homozygotes. Evidently the synergism detected by complete homozygosity for an autosome is variable.

Subvital homozygous radiated X chromosomes give results intermediate between homozygous and partially heterozygous autosomes, reflecting the lower genetic load (Table 6). The deviation from $a = 0$ is not immediately significant, but iteration gives

$$\hat{a} = 0.298 \pm 0.052$$

Supervital homozygous second chromosomes are partially recessive (Table 7), with

$$\hat{a} = 0.293 \pm 0.107$$

This is more nearly additive than the corresponding class of subvitals. The remaining two classes of supervitals (partially heterozygous second chromosomes and homozygous X chromosomes) are almost perfectly additive, with no finite maximum likelihood estimate ($\hat{a} \to \infty$).

TABLE 5

Analysis of subvital, partially heterozygous second chromosomes

Study	$a=0$				Among cultures df	$a=2$		$a=1.77$	
	ΣU_a	ΣK_{aa}	$(\Sigma U)^2/\Sigma K$	χ^2		ΣU_a	ΣK_{aa}	ΣU_a	ΣK_{aa}
Inbreeding experiment, $F=0$	14.827	85.6	2.57	324.16	239	1.076	2.0	1.592	2.8
Inbreeding experiment, $F=1/8$	49.107	102.5	23.53	298.87	244	—0.745	4.2	0.149	5.5
Inbreeding experiment, $F=1/4$	23.918	91.4	6.26	342.01	240	—4.147	4.3	—3.311	5.6
Inbreeding experiment, $F=1/2$	10.293	52.8	2.01	64.82	66	0.638	0.8	0.896	1.0
Postradiation (CHUNG 1962), $F=0$	13.904	46.0	4.20	190.82	174	0.479	1.3	0.738	1.9
Total	112.049	378.3	33.19	1220.68	963	—2.699	12.6	.064	16.8

Source	df	χ^2/σ^2
$a=0$	1	26.18
$F=0$ *vs.* $0<F<1/2$	1	2.03
$F<1/2$ *vs.* $F=1/2$	1	19.45
Residual among studies	3	2.22

$\sigma^2 = 1220.68/963 = 1.268$

DISCUSSION

WALLACE (1962) noted that long-persistent lethal and semi-lethal chromosomes are sometimes above average fitness in heterozygotes when tested within their own cultures. This is, of course, not unexpected from the way in which these chromosomes were ascertained (SPOFFORD 1963; CROW and TEMIN 1964). Such selected observations on chromosome segments are irrelevant to the average dominance of detrimental genes and provide no valid argument for heterotic lethals or against the practice of assessing heterozygous effects on an arbitrary genetic background. OSHIMA (1962) found that even long-persistent lethal

TABLE 6

Analysis of subvital homozygous X chromosomes

Study	$a=0$				Among cultures df	$a=.25$		$a=.30$	
	ΣU_a	ΣK_{aa}	$(\Sigma U)^2/\Sigma K$	χ^2		U_a	K_{aa}	U_a	K_{aa}
Basc radiated	—19.358	447.9	0.84	821.01	681	—19.521	212.9	—22.017	184.4
Canton-S radiated	29.927	441.7	2.03	938.64	729	24.450	207.8	21.154	179.4
Total	10.569	889.6	0.13	1759.65	1410	4.929	420.7	—0.863	363.8

Source	df	χ^2/σ^2
$a=0$	1	0.10
Between studies	1	2.20

$\sigma^2 = 1759.65/1410 = 1.248$

TABLE 7

Analysis of supervital homozygous second chromosomes

	a=0				Among cultures	a=.27		a=.30	
Study	ΣU_a	ΣK_{aa}	$(\Sigma U)^2/\Sigma K$	χ^2	df	ΣU_a	ΣK_{aa}	ΣU_a	ΣK_{aa}
HIRAIZUMI	8.461	180.2	0.40	57.29	40	—20.781	70.4	—21.886	63.8
Inbreeding experiment	19.747	29.7	13.13	157.18	109	16.819	14.7	15.233	13.6
Postradiation (CHUNG 1962)	5.255	21.0	1.32	99.97	91	5.970	10.7	6.084	9.9
Total	33.463	230.9	4.85	314.44	240	2.008	95.8	—0.569	87.3

Source	df	χ^2/σ^2
$a = 0$	1	3.70
Among studies	2	7.63

$\sigma^2 = 314.44/240 = 1.310$

chromosomes were deleterious in heterozygotes with normal chromosomes from the same population.

WALLACE (1959) reported that chromosomes irradiated with 500 r gave higher segregation frequencies than non-irradiated controls. He interpreted this as evidence for mutations which, although mostly deleterious in homozygotes, increased fitness in heterozygotes. Some alternative explanations are: (1) for one or more of the few chromosomes studied, radiation enhanced the probability of assortment in meiosis to the functional pole (NOVITSKI and SANDLER 1957); (2) survival from egg to adult was increased by radiation, but unmeasured components of fitness negatively correlated with survival were decreased; (3) the results

TABLE 8

Analysis of supervital, partially heterozygous second chromosomes

	a=0				Among cultures	a=.2		a=2.0	
Study	ΣU_a	ΣK_{aa}	$(\Sigma U)^2/\Sigma K$	χ^2	df	ΣU_a	ΣK_{aa}	ΣU_a	ΣK_{aa}
Inbreeding experiment, $F = 0$	6.464	88.5	0.47	298.50	226	13.324	48.7	5.534	1.4
Inbreeding experiment, $F = 1/8$	17.674	72.5	4.31	291.28	197	17.470	43.5	2.882	1.5
Inbreeding experiment, $F = 1/4$	9.606	59.6	1.55	280.02	187	12.195	34.2	2.757	1.3
Inbreeding experiment, $H = 1/2$	13.841	29.3	6.54	123.75	88	12.135	17.3	1.891	0.7
Postradiation (CHUNG 1962), $F = 0$	10.744	41.9	2.75	182.66	157	8.989	25.4	1.937	1.0
Total	58.329	291.8	11.66	1176.21	855	64.113	169.1	15.001	5.9

Source	df	χ^2/σ^2
$a = 0$	1	8.47
Among studies	4	2.88

$\sigma^2 = 1176.21/855 = 1.376$

TABLE 9

Analysis of supervital homozygous X chromosomes

Study	$a=0$					$a=2$	
	ΣU_a	ΣK_{aa}	$(\Sigma U)^2/\Sigma K$	Among cultures χ^2	df	ΣU	ΣK
Basc radiated	—10.587	464.7	0.24	825.69	744	3.157	2.8
Canton-S radiated	73.804	459.4	11.86	938.50	725	10.581	3.1
Total	63.217	924.1	4.32	1764.19	1469	13.738	5.9

Source	df	χ^2/σ^2
$a=0$	1	3.60
Between studies	1	6.48

$\sigma^2 = 1764.19/1469 = 1.201$

are not repeatable (FALK 1961). Later (1963) WALLACE reported that radiation depressed viability, except perhaps on a highly inbred background. CRENSHAW (1965) observed increased productivity of inbred female progeny of irradiated male Tribolium. In addition to the second and third alternative hypotheses mentioned above, his experiment is subject to the criticism that it provides no evidence that the reported effect is chromosomal or persistent for more than one generation.

Since our score for the null hypothesis that $a = 0$ is significantly positive, we have no indication of overdominance in our material. Chromosomes supervital or subvital in homozygotes tend to have the same effects in heterozygotes, and the degree of dominance (h) actually increases as the homozygous effect (s) approaches zero (Figures 1–3).

Our data provide a clear example of the way in which the precise techniques of Drosophila experiments can lead to erroneous conclusions about nearly panmictic populations. Drosophila geneticists rely sometimes blindly on techniques for making a selected chromosome completely homozygous. We see in Figure 1 how much this distorts estimates of dominance compared with partially heterozygous chromosomes, which are much more nearly additive in their effects on viability. Partial heterozygotes must mirror single genes better than completely homozygous chromosomes.

This evidence is fatal to KIMURA's principle of minimum genetic load (1960), according to which evolution tends to minimize the sum of the mutation load and the integral of the disequilibrium load over all generations. HALDANE (1957)

TABLE 10

Values of a *used in Figures 1–3*

Source	k	Subvitals	Supervitals
Homozygous chromosome II	.48	0	0.293
Partially heterozygous chromosome II	.48	1.774	∞
Homozygous radiated X	.46	0.298	∞

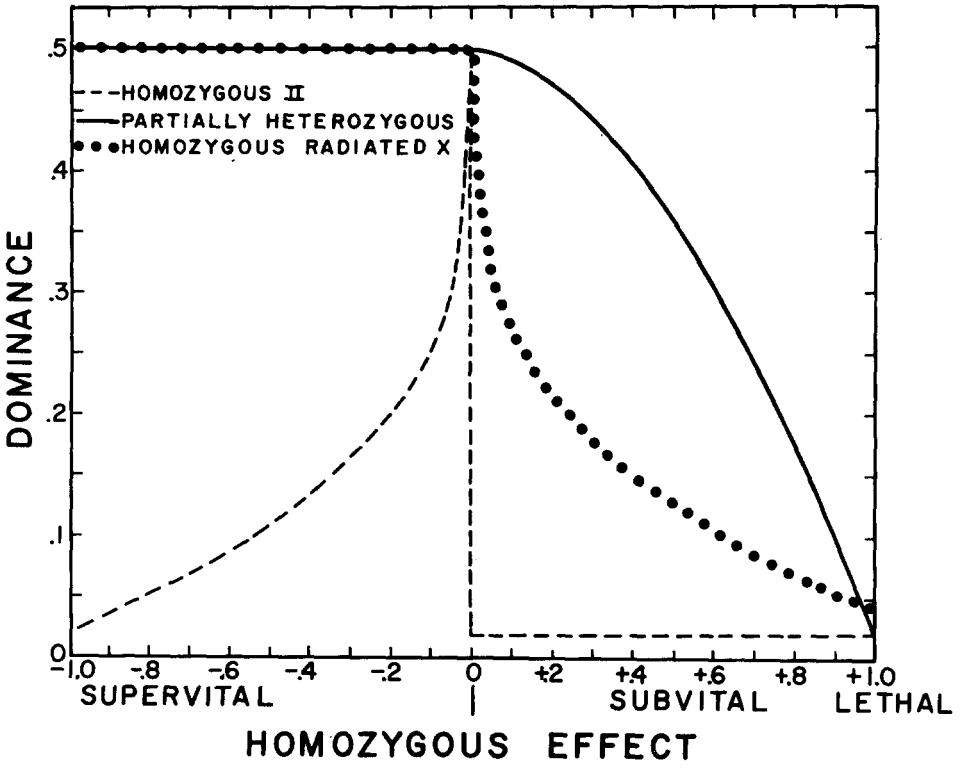

FIGURE 1.—Dominance (h) and homozygous effect (s).

called this integral the "cost of natural selection," which KIMURA changed to the "substitutional load." The term is unfortunate, since integration makes it only distantly related to other loads. KIMURA did not explain why he thought evolution should act in this mathematically curious way. However, we are concerned here not with the plausibility of the model but the validity of its conclusion, which is a relation among the total mutation rate (U), the total mutation load (U/z), the degree of dominance (h), the rate of allelic substitution (E), and the mean selection coefficient against homozygotes (s). KIMURA followed MORTON, CROW, and MULLER (1956) for the first three parameters, which as we have seen apply largely to lethal genes. For the rate of allelic substitution he took HALDANE's estimate of 1/300, which was based on the assumption that hypomorphic mutants measured in inbreeding studies and enumerated as lethals and subvitals are the raw material of evolution, that their dominance characterizes the evolutionary useful genes and does not change during the course of selection, and that the shift from subvitality to advantage occurs in a single generation and does not increase the population density. If, on the contrary, evolution tends to alter the frequencies of polymorphic genes, the rate of allelic substitution is greatly increased over HALDANE's calculation. Perhaps for this reason, KIMURA's estimate of $h = .02$, $s = .01$ is in error. If the mutation load is largely due to

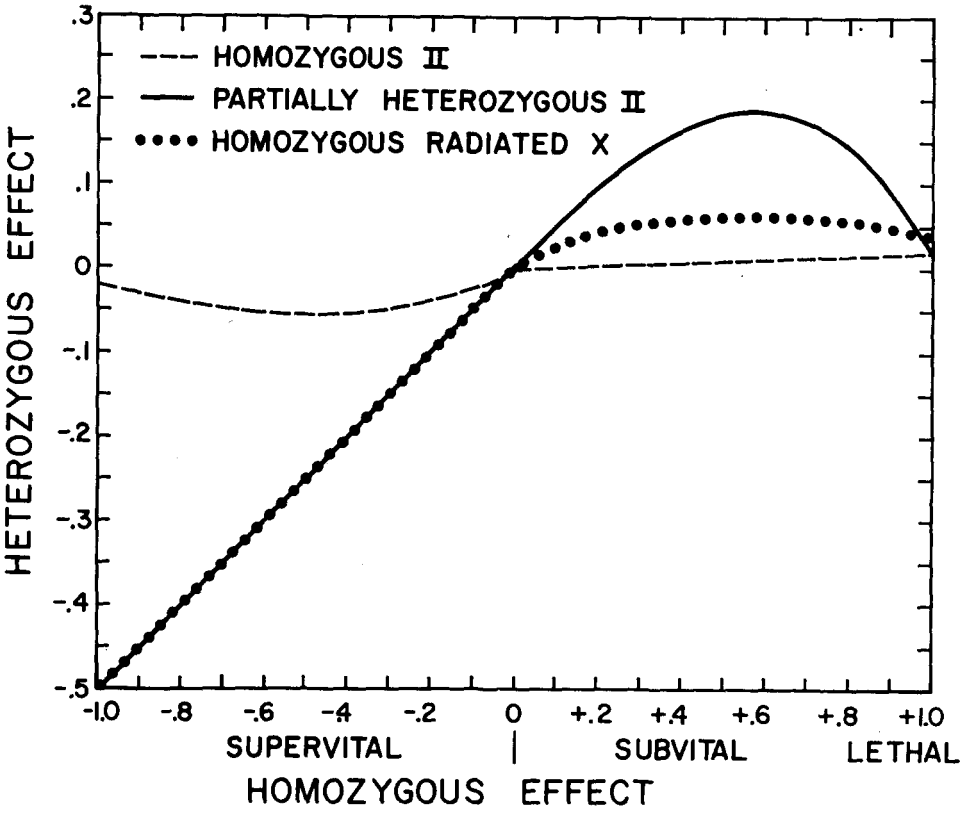

FIGURE 2.—Heterozygous effect *(hs)* and homozygous effect *(s)*.

lethals, the value of h is reasonable but s is much too small. If the load includes a large fraction of subvitals, the value of s may be appropriate but h is much too small. In either case, KIMURA's principle in its present form is invalid.

SUMMARY

Chromosomes supervital or subvital in homozygotes tend to have the same effects in heterozygotes, and the degree of dominance (h) approaches ½ as the homozygous effect (s) approaches zero. Dominance decreases at high levels of inbreeding. There is no evidence for overdominance. Our data are inconsistent with KIMURA's principle of minimum genetic load.

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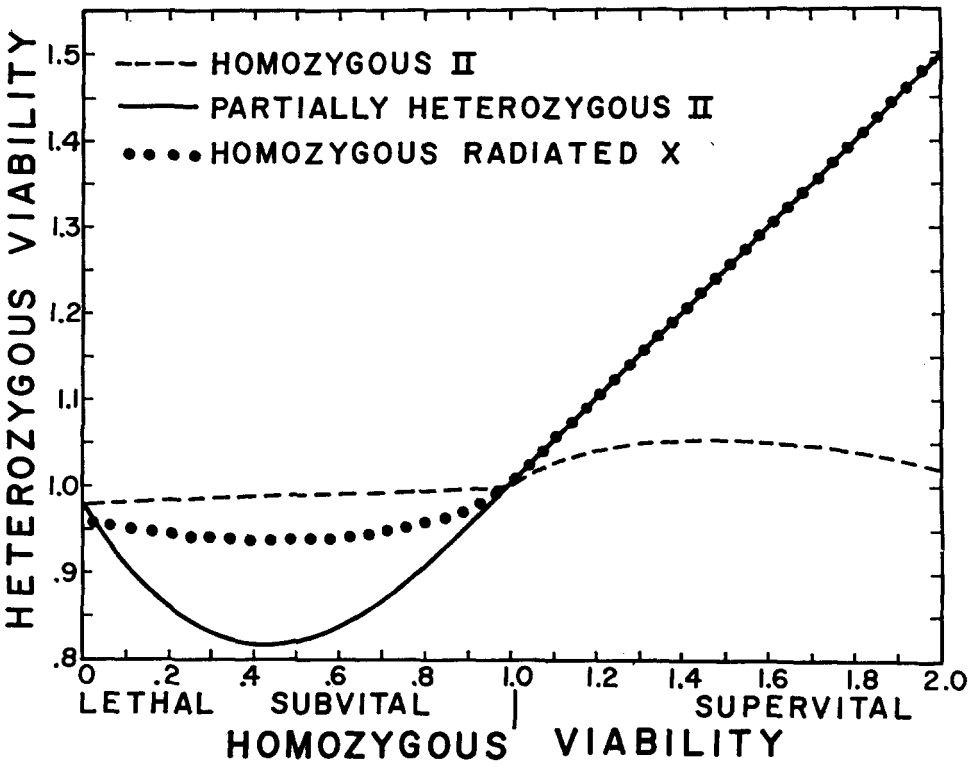

FIGURE 3.—Viability of heterozygotes (1–*hs*) and homozygotes (1–*s*).

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