gests that one may well expect the existence of such subspaces for biochemical kinetics *in vivo*. The study of this kinetics, if it represents a nonlinear system with finite amplitudes, can therefore be used to check the observational validity of the theoretical concepts introduced here (principle of finite classes: essentially sparse population of the phase space for any class of living systems).

Our general scheme permits us, moreover, to give a definition of the term organismic which is as purely formal as may be desired. We call a property of a class organismic if it exists in a finite universe of discourse but becomes lost when one goes to a corresponding infinite universe.

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THE NATURE AND STABILITY OF EQUILIBRIA UNDER OPTIMIZING SELECTION*

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Because of its presumably widespread occurrence, "optimizing selection," i.e., selection favoring individuals which are phenotypically intermediate, is of great interest in population biology. In particular it is important to know the extent to which such selection results in the long-term maintenance of genetic variability in populations. Early theoretical studies indicated that stable nontrivial gene frequency equilibria are not likely under intermediate optimum models of selection^{1, 2} and hence that optimizing selection is not favorable to maintenance of variability in an undivided panmictic population. Interest in optimizing selection was renewed by Kojima's³ demonstration that stable gene frequency equilibrium is possible under such selection, provided the phenotypic optimum value falls within a certain range of values determined by the degree of dominance on the underlying metric scale. Subsequently, Lewontin⁴ showed that, even when no permanent stable equilibrium of gene frequencies is predicted under free recombination, restriction of recombination can result in a quasi-stable equilibrium, i.e., linkage can promote the maintenance of genetic variability due to very slow rates of change in genotypic frequencies. Lewontin also demonstrated that optimum models generate significant amounts of "linkage disequilibrium" and there is now evidence that such linkage disequilibrium can have important effects on the position and stability of gene

frequency equilibria.⁵ In this paper we will show that linkage disequilibrium is influenced by the level of dominance, position of the optimum, linkage, and inbreeding and that population structure under optimizing selection can be understood only if all of these factors are taken into account.

Wright's² model of quadratic deviations from an intermediate optimum, in which the fitness of an individual falls off as the square of the deviation of its value from some optimum phenotype (Φ), will be considered first. This model has been described in detail by Kojima³ and Lewontin⁴ so that only the essential notation need be given here. Assume that genotypic value (y) on the primary metric scale is governed by two loci with two alleles each. Assume that the loci have equal effects and that they are linked with recombination value c . For each locus, say the j th, let the metric value be

$$\begin{array}{ccc} A_j A_j & A_j a_j & a_j a_j \\ 2\alpha & (1 + H)\alpha & \alpha, \end{array}$$

where H is a measure of dominance. Note that there is no epistasis on the primary scale. Let the fitness values w_{ij} of the nine possible genotypes be given by a function of $[-(y_{ij} - \Phi)^2]$, chosen suitably to give unity as the selective value of the most fit genotype. Following Lewontin and Kojima,⁶ equilibrium points under random mating are defined as $\Delta g_k = 0$, where the g_k 's are the gametic frequencies, g_{AB} , g_{Ab} , g_{aB} , and g_{ab} . Thus, we assume that our (w_{ij}) matrix is of the form

$$\begin{pmatrix} w_1 & w_2 & w_3 \\ w_2 & w_4 & w_5 \\ w_3 & w_5 & w_6 \end{pmatrix}, \text{ where } w_1 = \frac{K - (4\alpha - \Phi)^2}{K}, w_2 = \frac{K - (2\alpha + (1 + H)\alpha - \Phi)^2}{K},$$

and so forth, and K is an arbitrary constant. The equilibrium gametic frequencies $\hat{g}_k$, are given by the solutions of the simultaneous equations

$$g_1(w_1 g_1 + w_2 g_2 + w_3 g_3 + w_4 g_4 - \bar{W}) - cw_4 D = 0 \quad (1)$$

$$g_2(w_2 g_1 + w_3 g_2 + w_4 g_3 + w_5 g_4 - \bar{W}) + cw_4 D = 0 \quad (2)$$

$$g_3(w_3 g_1 + w_4 g_2 + w_5 g_3 + w_6 g_4 - \bar{W}) + cw_4 D = 0 \quad (3)$$

$$g_4(w_4 g_1 + w_5 g_2 + w_6 g_3 + w_6 g_4 - \bar{W}) - cw_4 D = 0. \quad (4)$$

In the equations (1)–(4), $D = \hat{g}_1 \hat{g}_4 - \hat{g}_2 \hat{g}_3$ is a measure of linkage disequilibrium and $\bar{W} = \sum w_{ij} g_k g_l$ is mean population fitness. When $D \neq 0$, $\bar{W}$ is a function not only of gene frequencies (q_1, q_2) at the two loci but also of D ; it follows, therefore, that the conditions given by Kojima³ in terms of $(\partial^2 \bar{W})/(\partial q_i^2)$ and $(\partial^2 \bar{W})/(\partial q_i \partial q_j)$ are not sufficient to specify stability when there is linkage disequilibrium. This was recognized by Kojima³ but the effect of linkage disequilibrium on the conditions for stable gene frequency equilibrium was regarded as trivial and hence ignored.

The conditions for stability of gene frequency equilibria can be established by solution of two simultaneous cubic equations in $\hat{g}_1$ and $\hat{g}_4$ because, by virtue of the symmetry between equations (2) and (3), $\hat{g}_2 = \hat{g}_3 = [1 - (\hat{g}_1 + \hat{g}_4)]/2$. Explicit solutions can be obtained using methods given by Kimura,⁷ or alternatively in terms of the latent roots of the Jacobian $\left(\frac{\partial \bar{W}}{\partial g_k}\right)$, as described by Hull.⁸ Generalizing to

include inbreeding in terms of a mixed mating system involving t per cent of out-crossing and $(1 - t)$ per cent of selfing leads to substantial complications because all nine genotypic frequency components must then be considered. We did not, therefore, attempt literal solutions, even for the random mating case, but instead determined gene frequency equilibria through numerical solutions on a digital computer. The stability of equilibria were tested by assuming different initial gene frequency vectors, or by causing small disturbances in the $\hat{g}_k$'s at equilibrium. The bounds on value of Φ for different types of equilibria were determined by plotting Φ at successive increments of 0.1.

Gene Frequency Equilibrium.—The conclusions regarding equilibrium situations reached from computations for 2- and 3-locus models, assuming random mating ($t = 1$) and free recombination ($c = 0.5$), are summarized in Figure 1. In this

FIG. 1.—Conditions on the optimum (Φ) and degree of dominance (H) for different types of gene frequency equilibria ($t = 1$, $c = 0.50$). For the 2-locus case, $1a$, $1b$ give stable equilibria with one locus polymorphic; $2a$, $2b$, both loci become fixed; $2c$, region of isoplethic equilibrium; 3 , region of stable equilibrium with $D \neq 0$; 4 , region also given as stable by Kojima's conditions. Regions 3^* and 4^* are the three-locus analogues to regions 3 and 4 .

figure the level of dominance, H , is represented on the abscissa and values of Φ , scaled in units of gene effect, α , appear along the ordinate. First, consider the 2-locus case for which the area bounded by $ABCD$ represents the combinations of Φ and H that allow nontrivial equilibrium involving one or both loci. The area outside $ABCD$ represents combinations of Φ and H for which both loci go to fixation. Four distinct regions can be distinguished within the area bounded by $ABCD$. In region $2c$ an equilibrium, with both loci unfixed, is attained only if the initial gene

frequencies are exactly equal at both loci ($p_1^{(0)} = p_2^{(0)}$). This equilibrium will persist only as long as the condition of exact equality of gene frequencies is satisfied. It is proposed that this special class of metastable equilibrium be termed *isoplethic*. If a population is in isoplethic equilibrium and there is a disturbance that causes gene frequencies to depart from equality, as must happen eventually in any real population, one locus goes to fixation while the other remains unfixed, giving a stable equilibrium in region 1*a*, or 1*b*. If the more recessive allele at one of the two loci becomes fixed (say, $p_1 = 0$, $q_1 = 1$), the population goes into equilibrium in region 1*a*. If, however, the dominant allele goes to fixation ($p_1 = 1$), the single-locus equilibrium falls in region 1*b*, i.e., the phenotypic values will be larger than in the preceding case by the amount 2α , representing the difference between $a_i a_i$ and $A_i A_i$.

Region 3 represents the combinations of Φ and H that lead to stable equilibrium with both loci unfixed; this region therefore involves linkage disequilibrium ($D \neq 0$). For $0 \leq H \leq 0.2$ there is no value of Φ which permits a nontrivial, stable equilibrium, but as H increases to an intermediate level of dominance, the shaded area (region 3) becomes wider, indicating there is wide range of values of Φ for which stable gene frequency equilibrium occurs with $D \neq 0$. Note that region 3 lies above the intermediate phenotypic value, $y = 2$, and hence corresponds to overdominance on the secondary or fitness scale. With further increases in H the shaded area rapidly disappears, so that for $0.95 < H \leq 1.0$ there is no region 3. The lower bound of region 3 coincides exactly with the lower bound given by Kojima³ and Lewontin.⁴ The upper bound is, however, lower than indicated by these investigators. Correct placement of the upper bound cuts off an area which is designated as region 4 in Figure 1. Region 4 represents the effect of D on conditions for stability and it shows that ignoring linkage disequilibrium leads to substantial overestimation of the region of stability.

The requirements for stable equilibrium with larger numbers of loci, each with additive effect α and dominance H , follow a straightforward pattern which can be adequately illustrated by the three-locus case (Fig. 1). Regions 3* and 4*, giving stable equilibria with all three loci unfixed, correspond to regions 3 and 4 of the two-locus case. The restriction on Φ which results from taking D into account, represented by region 4*, is similar in magnitude to that for the two-locus case. The effects of the addition of successively larger numbers of loci to the system can be depicted as a series of regions comparable to regions 3* and 4*. The effect of adding each successive locus is to shift the corresponding region upwards along the ordinate by an amount 2α .

With increase in the number of loci the isoplethic region 2*c* becomes progressively wider, and the 4, 5, . . . , n locus stable regions corresponding to region 3* depart farther and farther from the intermediate range of values of Φ . In other words, to maintain successively larger numbers of loci in stable equilibrium, the optimum phenotype must approach more and more closely the extreme phenotype that is possible.⁴ Results with the three-locus case illustrate how, for a given level of dominance, the value of Φ affects the number of loci that can be maintained unfixed. Consider populations with initial gene frequencies $p_1^{(0)} > p_2^{(0)} = p_3^{(0)}$ and $H = 0.6$. With $\Phi = 4.9\alpha$ the equilibrium population has specifications $0 < \hat{p}_1 = \hat{p}_2 = \hat{p}_3 < 1$ and $D_{12} = D_{23} = D_{13} = -0.00145$, i.e., the population comes to stable

equilibrium with all three loci unfixed (region 3*). With $2.8 \alpha < \Phi \leq 4.8 \alpha$ equilibrium occurs in region 3 ($\hat{p}_1 = 0$, $0 < \hat{p}_2 = \hat{p}_3 < 1$), i.e., stable 3-locus equilibrium does not occur when Φ takes intermediate values. Instead, there is a decay to the next lower or 2-locus stability level. With $\Phi < 2.8 \alpha$ equilibrium occurs in region 2c, i.e., with $\hat{p}_2 = \hat{p}_3 \neq 0$ or 1. This is a region of isoplethic equilibrium, and in any real situation chance deviation of gene frequencies from exact equality would lead to decay to a single-locus stable equilibrium falling either in region 1a or in region 1b.

Effect of Inbreeding and Linkage on Conditions for Stability.—The bounds on region 3 for the two-locus case, assuming random mating ($t = 1$) and free recombination ($c = 0.50$), are given in the top row of Table 1. This table also gives the

TABLE 1
EFFECT OF LINKAGE AND INBREEDING ON THE RANGE OF OPTIMUM VALUES (Φ) UNDER WHICH STABLE EQUILIBRIA OCCUR*

Proportion of out-crossing t	Recombination value c	Lower (L) and Upper (U) Bounds on Φ Scaled in Units of Gene Effect, α									
		$H = 0.2$		$H = 0.4$		$H = 0.6$		$H = 0.8$		$H = 0.9$	
		L	U	L	U	L	U	L	U	L	U
1.0	0.50	None		3.0	3.5	3.0	3.7	3.0	3.5	3.1	3.5
1.0	0.10	3.3	3.5	3.0	3.6	3.0	3.7	3.0	3.7	3.1	3.6
1.0	0.01	2.5	3.5	2.6	3.6	2.7	3.7	2.9	3.7	3.1	3.6
0.50	0.50	None		None		None		None		None	
0.50	0.10	None		3.2	3.2	None		None		None	
0.50	0.01	2.5	3.2	2.6	3.2	2.7	3.1	2.9	3.0	3.0	3.1
0.05	0.50	None		None		None		None		None	
0.05	0.10	None		None		None		None		None	
0.05	0.01	2.5	3.0	2.5	3.0	2.7	3.0	2.9	3.0	3.0	3.0

* There is no value of Φ which gives stable equilibrium with $D \neq 0$ when there is no dominance ($H = 0$), or when dominance is complete ($H = 1$).

effects of inbreeding and linkage on the region of stability. The general effect of closer inbreeding is a restriction of the bounds of region 3, whereas tighter linkage has the opposite effect. The effect of linkage is not the same for various levels of inbreeding. For example, the difference between $t = 1.0$ and $t = 0.05$ is rather small in terms of the extent of region 3 when linkage is tight but it is very large under relatively loose linkage.

TABLE 2
SOME POPULATION PARAMETERS* FOR A SAMPLE OF EQUILIBRIUM POPULATIONS WITH $D \neq 0$

	c	H	Φ	D	$\bar{w}$	$\hat{p}_1 = \hat{p}_2$	Observed $\hat{R}$	Expected R
1.0	0.01	0.6	{ 3.0	-0.0893	0.9700	0.6713	0.4486	0.4413
			{ 3.5	-0.0047	0.9883	0.9191	0.1503	0.1487
1.0	0.01	0.8	{ 3.0	-0.0782	0.9593	0.6753	0.4433	0.4385
			{ 3.5	-0.0019	0.9873	0.9364	0.1201	0.1191
1.0	0.50	0.6	{ 3.0	-0.0033	0.9632	0.7632	0.3682	0.3545†
			{ 3.5	-0.0002	0.9881	0.9277	0.1354	0.1351
1.0	0.50	0.8	{ 3.0	-0.0022	0.9553	0.7682	0.3362	0.3259†
			{ 3.5	-0.0001	0.9872	0.9388	0.1159	0.1150
0.50	0.01	0.6	{ 2.8	-0.2121	0.9693	0.5285	0.3400	0.3322
			{ 3.0	-0.1025	0.9620	0.6725	0.3042	0.2937
0.50	0.01	0.8	{ 2.9	-0.1913	0.9572	0.5510	0.3349	0.3291†
			{ 3.0	-0.0967	0.9547	0.6811	0.2963	0.2896
0.05	0.01	0.6	{ 2.8	-0.2458	0.9652	0.5026	0.0498	0.0474†
			{ 3.0	-0.1058	0.9470	0.6740	0.0455	0.0416†
0.05	0.01	0.8	{ 2.9	-0.2388	0.9558	0.5052	0.0480	0.0463†
			{ 3.0	-0.1003	0.9459	0.6819	0.0435	0.0402†

* Meaning of symbols is given in the text and in Fig. 1; $\hat{p}_1$, $\hat{p}_2$ refer to equilibrium gene frequencies, and $\hat{R}$ to the frequency of heterozygotes at equilibrium. The expected frequency of heterozygotes is given by $2\hat{p}\hat{q}(1-F)$, where $F = (1-t)/(1+t)$.

† Nearly at equilibrium.

Some General Features of Equilibrium Populations.—Table 2 gives the linkage disequilibrium parameter (D), mean population fitness ($\bar{W}$), equilibrium gene frequencies ($\hat{p}_1, \hat{p}_2$), and observed and expected levels of heterozygosity (R) for a sample of populations with varying specifications regarding level of inbreeding, linkage, dominance, and position of the optimum. As expected with an optimum model, D is always negative indicating an excess of repulsion type (Ab, aB) gametes. Also as expected, this effect becomes increasingly pronounced with tighter linkage⁴ and heavier inbreeding.⁵ In all cases $\bar{W}$ is quite close to the maximum possible value of unity. Equilibrium gene frequencies tend to be intermediate with tight linkage. Thus, as pointed out by Lewontin,⁴ linkage promotes proportionately greater variance per locus, and closer inbreeding tends to have effects that are similar to those of tighter linkage.⁵ An important point to note from Table 2 is that heterozygosity at each of the two loci is higher than predicted from the relationship, $2\hat{p}\hat{q}$ ($1 - F$). Marginal overdominance, however small it may be in magnitude, seems to be a necessary condition for stability of equilibria for optimum models.³ This observation also agrees with our earlier findings for a greater variety of epistatic models.⁵

Effect of Heterozygote Advantage on Stability.—The effect of overdominance on the primary scale has been investigated by Kojima³ who found that with $H > 1$ there is a wide range of values of Φ which lead to stable equilibrium with both loci unfixed. Our results from simulation differ from Kojima's results only in detail. When linkage disequilibrium is taken into account, there is some restriction of the lower bound of the region of stability. This restriction is analogous to that which occurs in the upper bound when H is in the partial dominance range ($H < 1$).

The effect of overdominance on the secondary scale has been investigated by Wright⁹ who assumed in certain of his models that heterozygotes are superior in fitness to homozygotes. This is equivalent to adding an heterotic increment, say, β , to all heterozygotes giving a (w_{ij}) matrix of the form

$$\begin{pmatrix} w_1 & w_2 + \beta & w_3 \\ w_2 + \beta & w_4 + 2\beta & w_5 + \beta \\ w_3 & w_5 + \beta & w_6 \end{pmatrix}.$$

The effect of the β -component on stability conditions is illustrated in Table 3, which gives lower and upper bounds

LOWER (L) AND UPPER (U) BOUNDS ON Φ FOR $D \neq 0$ (REGION 3) FOR A 2-LOCUS MODEL, WITH HETEROTIC INCREMENT, β																						
β	t	c	$H = 0$		$H = 0.2$		$H = 0.4$		$H = 0.6$		$H = 0.8$		$H = 0.9$		$H = 1.0$							
			L	U	L	U	L	U	L	U	L	U	L	U	L	U						
0.05	1.0	0.50	2.5	3.9	2.3	4.0	2.4	4.0	2.6	4.0	2.7	4.0	2.8	4.0	2.9	4.0						
0.10	1.0	0.50	0.1	4.0	0.6	4.0	1.6	4.0	2.0	4.0	2.3	4.0	2.5	4.0	2.6	4.0						
0.10	0.50	0.50	3.1	3.7	2.5	3.7	2.5	3.9	2.6	4.0	2.7	4.0	2.8	3.1	2.8	3.1						
0.10	0.05	0.50																				
0.10	0.05	0.15	1.0	3.0	1.0	3.0	2.0	3.0	2.3	3.0	2.6	3.0	2.7	3.0	2.8	3.0						
0.10	0.05	0.01	1.0	3.0	1.0	3.0	1.0	3.0	1.2	3.0	1.8	3.0	2.0	3.0	2.2	3.0						
																		Region 3 absent			→	

For meaning of symbols, see the text or Fig. 1.

on Φ for different levels of dominance on the primary scale, and for different values of β . Under random mating and free recombination the region of stability corresponding to region 3 of Figure 1 extends, as β increases, over an increasing range of values of H and Φ . With $\beta = 0.10$, the upper bound of region 3 reaches the maximum possible phenotypic value, that of the double heterozygote $AaBb$. Under inbreeding the region of stability is also larger on its lower bound than the region obtained without the β increment (Table 1). However, $\beta = 0.10$ seems to be an inadequate level of heterozygote advantage to prevent disappearance of the region of stability under heavy inbreeding (e.g., $t = 0.05$) with free recombination ($c = 0.50$).

We have investigated two asymmetrical models (Tables 4 and 5) to determine the effect of selective dif-

TABLE 4
SELECTIVE VALUES OF GENOTYPES* IN MODEL 1,
AFTER WRIGHT⁹

	<i>AA</i>	<i>Aa</i>	<i>aa</i>
<i>BB</i>	0.64	1.00	0.96
<i>Bb</i>	1.00	1.05	1.00
<i>bb</i>	0.94	1.00	0.64

* The frequencies of alleles *A,a* and *B,b* are denoted by p_1, q_1 and p_2, q_2 in this paper. Wright denoted the equivalent frequencies by $1-p, p$ and $1-q, q$.

TABLE 5
SELECTIVE VALUES OF GENOTYPES* IN MODEL 2

	<i>AA</i>	<i>Aa</i>	<i>aa</i>
<i>BB</i>	0.59	1.00	0.91
<i>Bb</i>	1.00	1.05	1.00
<i>bb</i>	0.89	1.00	0.59

* See footnote, Table 4.

ferences between homozygotes on the capacity of mixed optimum-heterotic selection to maintain genetic variability. Note that selective values in these models do not fall off strictly as quadratic deviations from the optimum. Table 4 shows a set of selective values in which the homozygotes are at disadvantages of 4 and 6 per cent, respectively, relative to the single heterozygotes. This model (here designated Model 1) is due to Wright¹⁰ who determined equilibrium gene frequencies analytically, ignoring linkage disequilibrium. His solutions for $t = 1, c = 0.50$ were (a) $\hat{q}_1 = \hat{p}_2 = 0.746$, (b) $\hat{q}_1 = \hat{p}_2 = 0.158$, and (c) $\hat{q}_1 = \hat{p}_2 = 0.548$, corresponding to a two-peaked adaptive topography with (a) and (b) representing stable gene frequency equilibrium points and (c) an unstable saddle point. When linkage dis-

Item*		TABLE 6 STABLE EQUILIBRIA UNDER MODELS 1 AND 2									
		Model 1—					Model 2—				
		Recombination Value, <i>c</i>					Recombination Value, <i>c</i>				
1.0	$\hat{p}_1 = \hat{q}_2$	0.50	0.25	0.10	0.01	0.50	0.25	0.10	0.01	0.50	0.25
	$\hat{p}_1$	0.1764	0.2129	0.3995	0.4534	0.4061	0.4418	0.4633	0.4718	0.4061	0.4418
	$\hat{p}_1$	0.9713	0.9725	0.9792	0.9962	0.9541	0.9577	0.9646	0.9766	0.9541	0.9577
	<i>D</i>	-0.0041	-0.0121	-0.0599	-0.1664	-0.0152	-0.0296	-0.0592	-0.1443	-0.0152	-0.0296
0.50	$\hat{p}_1 = \hat{q}_2$	0	0	0	0	0	0	0	0	0	0
	$\hat{p}_1$	0.96	0.96	0.96	0.9813	0.91	0.91	0.9326	0.9495	0.91	0.91
	$\hat{p}_1$	0	0	0	0	0	0	0	0	0	0
	<i>D</i>	0	0	0	-0.2199	0	0	-0.1159	-0.2218	0	0

* $\hat{p}_1, \hat{q}_2, \bar{w},$ and *D* represent equilibrium gene frequencies, mean population fitness, and linkage disequilibrium values, respectively.

equilibrium is taken into account, it is found that there is only a single equilibrium point located at $\hat{q}_1 = \hat{p}_2 = 0.1764$. The effects of linkage on this model are to cause the equilibrium gene frequency point to shift toward more intermediate values and to increase linkage disequilibrium and mean population fitness (Table 6). Unless linkage is very tight, the effect of inbreeding is the fixation of the more fit homozygote.

Model 2 (Table 5) differs from Model 1 in that β is larger, i.e., there is greater heterozygote advantage on the secondary scale. This increased heterozygote advantage causes the populations to come to equilibrium at more intermediate gene frequencies than with Model 1. It also leads to increased linkage disequilibrium and frequently to avoidance of fixation under inbreeding, particularly with tight linkage.

Conclusions and Summary.—Wright's quadratic deviation model of optimizing selection was investigated to determine the joint effects of the position of the optimum, level of dominance, linkage, inbreeding, and heterozygote advantage on the nature and stability of gene frequency equilibria. Level of dominance on the primary scale governs the range of values of the optimum under which stable nontrivial equilibria involving two or more loci are possible. Restriction of recombination widens this range while inbreeding restricts it. Heterozygote advantage on the fitness scale, particularly in combination with tight linkage, leads to stable equilibrium under a very wide range of optimum values. This effect is relatively greater under inbreeding than under random mating. The values of the parameters of optimizing selection which permit stable nontrivial gene frequency equilibria often fall into ranges which are biologically reasonable. Optimizing selection therefore appears to be favorable for the long-time maintenance of genetic variability, even in undivided populations. As shown by Wright,^{2, 10, 11} prospects for long-term maintenance of genetic variability are expected to be even greater in populations subdivided into partial isolates.

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