Ever since the abnormalities of runt disease were first described they have repeatedly been compared to those observed in patients with certain lymphomas (*17*). Various theories have been propounded as to how maternally transmitted graft-versus-host reactivity might lead to the development of these tumors. In mice it has been established that graft-versus-host reactivity may result in a high incidence of lymphomas (*18*). Recent analysis indicates that this graft-versus-host reactivity unmasks and activates normally latent and undemonstrable oncogenic viruses (*19*). The work we describe in this article may have some relevance to the possible clinical significance of transplacental cellular mobility in man. We suggest that the relatively high incidence of lymphomas in children might also be, in part at least, due to unmasking of oncogenic viruses by subclinical graft-versus-host reactivity mediated by immunocompetent cells of maternal origin. The statistical evidence that male infants are at greater risk than females (*20*) is concordant with our observation that maternally induced runts include a significantly higher proportion of males than females (*10*).

References and Notes

1. A. E. Beer and R. E. Billingham, *Advan. Immunol.* **14**, 1 (1971).
2. A. E. Beer, R. E. Billingham, R. A. Hoerr, *Transplantation Proc.* **3**, 609 (1971).
3. J. deGrouchy and C. Trebuchet, *Bull. Eur. Soc. Hum. Genet.* **4**, 65 (1970); J. Walkanowska, F. A. Coute, M. M. Grumbach, *Lancet* **1969-I**, 1119 (1969).
4. J. T. Lanman, *J. Pediat.* **66**, 525 (1965).
5. D. R. S. Kirby, in *Human Transplantation*, F. T. Rapaport and J. Dausset, Eds. (Grune & Stratton, New York, 1968), p. 565; G. A. Currie, W. Van Doorninck, K. D. Bagshawe, *Nature* **219**, 191 (1968).
6. K. E. Hellström, I. Hellström, J. Brawn, *Nature* **224**, 914 (1969); K. E. Hellström and I. Hellström, in *Ontogeny of Acquired Immunity* (Ciba Foundation Symposium) (North-Holland, Amsterdam, 1972).
7. J. B. Solomon, *Frontiers Biol.* **20**, 75 (1971).
8. R. E. Billingham, L. Brent, P. B. Medawar, *Phil. Trans. Roy. Soc. London Ser. B* **239**, 357 (1956).
9. R. E. Billingham and L. Brent, *ibid.* **242**, 439 (1959).
10. A. E. Beer, R. E. Billingham, S. L. Yang, *J. Exp. Med.* **135**, 808 (1972).
11. R. E. Billingham and W. K. Silvers, *J. Exp. Zool.* **161**, 413 (1966).
12. W. K. Silvers, D. Lubaroff, D. B. Wilson, D. Fox, *Science* **167**, 1264 (1970); J. W. Streilein, I. Zeiss, D. Steinmuller, *Transplantation* **10**, 1264 (1970); E. M. Lance, E. A. Boyse, S. Cooper, E. A. Carswell, *Transplantation Proc.* **3**, 864 (1971).
13. J. I. Kadowaki, W. W. Zuelzer, A. S. Brough, R. I. Thompson, P. V. Wooley, D. Gruber, *Lancet* **1966-II**, 1152 (1966); W. L. Elkins, *Progr. Allergy* **15**, 78 (1971).
14. J. Palm, *Transplantation Proc.* **2**, 162 (1970).
15. C. F. Barker and R. E. Billingham, *ibid.* **3**, 172 (1971).
16. W. K. Silvers and R. E. Billingham, *J. Exp. Zool.* **161**, 413 (1966).
17. H. S. Kaplan and D. W. Smithers, *Lancet* **1959-II**, 1 (1959); A. C. Aisenberg, *N. Engl. J. Med.* **270**, 617 (1964).
18. R. S. Schwartz and L. Beldoti, *Science* **149**, 1511 (1965); R. W. Walford, *ibid.* **152**, 78 (1966).
19. M. S. Hirsch, S. M. Phillips, C. Solnick, P. H. Black, R. S. Schwartz, C. B. Carpenter, *Proc. Nat. Acad. Sci. U.S.A.*, in press; R. S. Schwartz, *Lancet* **1972-I**, 1266 (1972).
20. N. J. Smith, V. C. Vaughan, L. K. Diamond, in *Textbook of Pediatrics*, W. E. Nelson, Ed. (Saunders, Philadelphia, 1959), p. 990.

21. Supported in part by PHS grant A1-10678. We thank Bill Sanders for technical assistance and Dr. J. Wayne Streilein for advice and criticism.

Gene Flow and Population Differentiation

Studies of clines suggest that differentiation along environmental gradients may be independent of gene flow.

John A. Endler

Since the time of Darwin and Wallace there has been considerable interest in how species come to be different in different parts of their geographic ranges. Geographic isolation and spatial differences in environmental factors are thought to lead to the observed geographic differentiation within species, and may finally lead to speciation, when sexual and geographic isolation become complete (*1–3*). Differentiation into species is usually assumed to be impossible without barriers because gene flow is supposed to "swamp out" any differences evolved in response to local environmental factors (*1–9*).

Ehrlich and Raven (*10*), and the proponents of sympatric speciation (*11*) take exception to the view of the dedifferentiating effect of gene flow, and recent experiments (*12, 13*) and theoretical studies (*14, 15*) suggest that gene flow may not have as great an effect as has been postulated. The possibility of parapatric divergence is less commonly discussed (*1, 3, 16, 17*) and is usually assumed to have the same problems that are inherent in sympatric speciation, in particular the difficulty of accounting for the evolution of sexual isolation in the face of considerable gene flow (*1*). The crucial question is how much does gene flow actually retard the development of geographic differentiation within a species (*2*). In this article I present experimental and theoretical evidence suggesting that the effect of gene flow may be small.

Huxley (*17*) defined a cline as a gradient in a measurable character. Relative to the dispersal rate of a species, the slope of a cline between regions is indicative of the extent to which the inhabitants have differentiated. A steep cline means sharp differentiation, as in the pelage colors of the deermouse, *Peromyscus maniculatus* (*18*), and gentle clines mean indistinct divergence between areas, as in the plumages of many duck species (*19*). The basis of subspeciation and speciation is geographic variation in gene frequencies. For a polymorphic character (*20*) a cline is a temporally stable gradient of geotype or gene frequencies.

In spite of the number of clines that have been described (*1, 17, 21, 22*), there is a dearth of natural systems for which all the necessary ecological information has been recorded for each morph along a cline. Therefore I chose to study a model system that could be investigated both experimentally and theoretically. I discuss here a hypotheti-

The article was written while the author was National Science Foundation graduate fellow in the department of zoology, University of Edinburgh, Edinburgh, Scotland. The author's present address is Department of Biology, Princeton University, Princeton, New Jersey 08540.

cal diploid species distributed as a series of discrete breeding units, or demes. A stepping-stone model of dispersal (gene flow per generation to adjacent demes only) is incorporated because, for most field estimates, breeding sites are localized, and individuals dispersing from a given deme are unlikely to move beyond the adjacent demes within one generation. Those individuals that do move longer distances before settling are unlikely to become established and breed in the new area for many reasons (*10, 22–24*). This model is a closer approximation to the discontinuous distribution and limited gene flow patterns observed for many species (*22–24*) than is provided by the neighborhood model (*6*). A deme may be regarded as a spatially discrete breeding unit—an effectively panmictic aggregate of organisms lasting for at least one breeding session and connected by gene flow before and after reproduction. A given deme exchanges a given percentage, g, of its mature or breeding members with the neighboring demes each generation. The model was investigated by experimentation with *Drosophila melanogaster* and by computer simulation.

Experimental Clines in *Drosophila melanogaster*

In order to study the effects of known gene flow and selection, a series of clines were set up in *Drosophila melanogaster*, made polymorphic for *Bar* by introducing this gene and a small segment of the adjacent X chromosome into a large population (approximately 8000) of outbred "normal" flies, originating from Robertson's "Standard Kaduna" population cage. (Standard Kaduna is a large outbred population of *D. melanogaster* collected at Kaduna, North Africa, and maintained for many years.) Five sets (A through E) of 15 demes each were made up from the Bar-Kaduna population. Initially each deme contained 50 pairs of flies with a *Bar* gene frequency of 50 percent. These were allowed to mate and produce offspring for one generation (generation 0) before selection and gene flow were started. This and all subsequent generations were raised in glass vials (30 by 100 millimeters) stoppered with cotton, each vial containing about 17 milliliters of cornmeal-molasses-agar medium. Generations were discrete.

The arrangement of artificial selection and gene flow in the five sets is shown in Table 1. Each deme in each generation was subjected to (i) collection and scoring of emerging adults for each of 6 days; (ii) artificial selection (if any) on each genotype; (iii) reduction of populations to $N = 50$ pairs per deme, genotype frequencies being held constant; (iv) gene flow (if any); (v) a mating period of 24 hours; (vi) an egg-laying period of 4 days; and (vii) a developmental period at $25° \pm 1°C$, ending with emergence of next-generation adults. Differences in fitness resulted in the occurrence of *natural* selection against the *Bar* genotypes during period (vii). This natural selection must be distinguished from the artificial selection of Table 2.

Table 1. The arrangement of selection and gene flow.

Set	Artificial selection	Gene flow	Control
A	Yes	Yes	
B	Yes	No	For gene flow
C	Yes	Yes	
D	Yes	No	For gene flow
E	No	Yes	For artificial selection

To produce clines, the artificial selection was imposed in the form of a gradient across the deme series, with an increment in selection between adjacent demes of $I = 0.04$. The demes in sets A, B, C, and D were subject to the absolute survival values shown in Table 2. The symbol x represents any location of a deme within a series; d is the total number of demes in a series. In each deme, the parents of the next generation were chosen according to Table 2 as follows. Taking males and females separately, a fraction $W_1(x)$, of the total number of flies in the deme in position x consisted of *Bar* genotypes; a fraction $W_2(x)$ consisted of heterozygotes (females only as *Bar* is sex-linked), and $W_3(x)$ consisted of "normal" genotypes. *Bar* is treated as a dominant gene for the purposes of artificial selection. The null point (*25*) in the artificial selection was located at deme 3 because a preliminary estimate suggested that this selection pattern would uniformly counteract the natural selection against *Bar*, centering the resulting clines near deme 8. Artificial selection (Table 2) was continued in generations 1 through 35, except in generation 10 when no selection was made, and in generation 18 when females only were selected.

Table 2. Artificial selection in the experimental clines: proportions of each genotype surviving in each deme.

Deme position (x)	$W_1(x), W_2(x)$	$W_3(x)$
1	0.42	0.58
2	.46	.54
3	.50	.50
4	.54	.46
5	.58	.42
6	.62	.38
7	.66	.34
8	.70	.30
9	.74	.26
10	.78	.22
11	.82	.18
12	.86	.14
13	.90	.10
14	.94	.06
15	.98	.02

Gene flow was accomplished in each deme by removing $g = 0.40$ of each genotype from a given deme and placing one half of these emigrants (that is, 20 percent of N) into the deme on the left and the remaining half of the emigrants into the deme on the right. Thus adjacent demes exchanged 20 percent of their members, and a given deme contained 40 percent immigrants after gene flow each generation. The would-be emigrants from the end demes, 1 and 15, were returned to the deme from which they came.

The clines for gene frequency in generation 35 are shown in Fig. 1, and the slopes of the clines in all generations are shown in Fig. 2. Gene frequencies are calculated on the total number of eclosing adults from each deme, and the slope of a cline is the regression of gene frequency on deme number for the set concerned.

The response to selection (sets A through D) was quite marked for the first five or six generations; thereafter there was little change in the configurations of the clines. All slopes became significantly different from zero at generation 1, with the exception of set E (no selection) which became significantly different from zero in generation 4. Thereafter the slopes of sets A through D remained significantly different from zero and the slope of set E remained insignificant. There is no consistent or significant difference between the selective clines with 40 percent gene flow (A and C) and those without gene flow (B and D) from generation to generation; thus the effect of gene flow in the experiment is not detectable.

Models of Clines

A cline may result from one or more of four basic situations; random genetic sampling drift, secondary contact between formerly isolated populations, spatially discontinuous changes of environment, and continuous environmental gradients. Theory suggests that the slopes of clines produced by genetic drift fall off rapidly with increasing gene flow. For any significant and stable differentiation to evolve as a result of drift the absolute number of dispersing individuals (mN) must be less than one per generation (*6, 9*). This restriction is unlikely to be achieved in nature, and there is a very low probability that all genotypes will have exactly the same mean survival values for even a short period of time; therefore clines produced by genetic drift will not be considered here. Secondary contact between differently structured populations will only produce clines under special circumstances, and will be discussed elsewhere (*26*).

The effects of gene flow on clines resulting from sharp environmental differences have been discussed by several authors (*7, 14, 15, 27*). If there is a large difference in selective effects between two environments, then even large amounts of gene flow are unable to prevent the formation of steep clines (*14, 15*). Given a smoothly changing environmental factor, which is probably more common in nature than are sharp changes (*1, 24, 28*), there are several configurations that will produce a cline; four will be discussed here.

In each of the following models the symbols $W_1(x)$, $W_2(x)$, and $W_3(x)$ represent the probabilities of survival of the three genotypes of an autosomal locus, AA, Aa, and aa, from zygote to reproduction in each deme (*29*). Their values are dependent upon the location in the deme series, x, and form selection gradients along the series. Equilibrium of the A gene frequencies, $\hat{p}$, measured after selection and gene flow, will result from many generations of random mating, selection (W's), and stepping-stone gene flow along the linear series of d demes. The amount of gene flow will be represented by g, the total fraction of immigrants from both adjacent demes within a given deme after gene flow in a given generation. As in the experimental clines ($g = 0.40$, $d = 15$), the would-be emigrants from the end demes (1 and d) return to the deme from which they came (*30*). Thus the models differ from the experimental systems A and C only in that there is no second period of selection (no "natural" selection) before the measurement of gene frequencies. This simplification will bias the models in favor of the attenuating effects of gene flow.

The *gradient model*, 1, as in the experiments, incorporates survival functions, $W_1(x)$, $W_2(x)$, and $W_3(x)$, for genotypes AA, Aa, and aa, respectively, which are dependent only upon the position, x, in the deme series, in which the genotypes were born (Fig. 3a). Such would be the case if, for example, the probability of survival of a particular genotype increased with position along a transect up a mountainside, and the probabilities of survival of the other

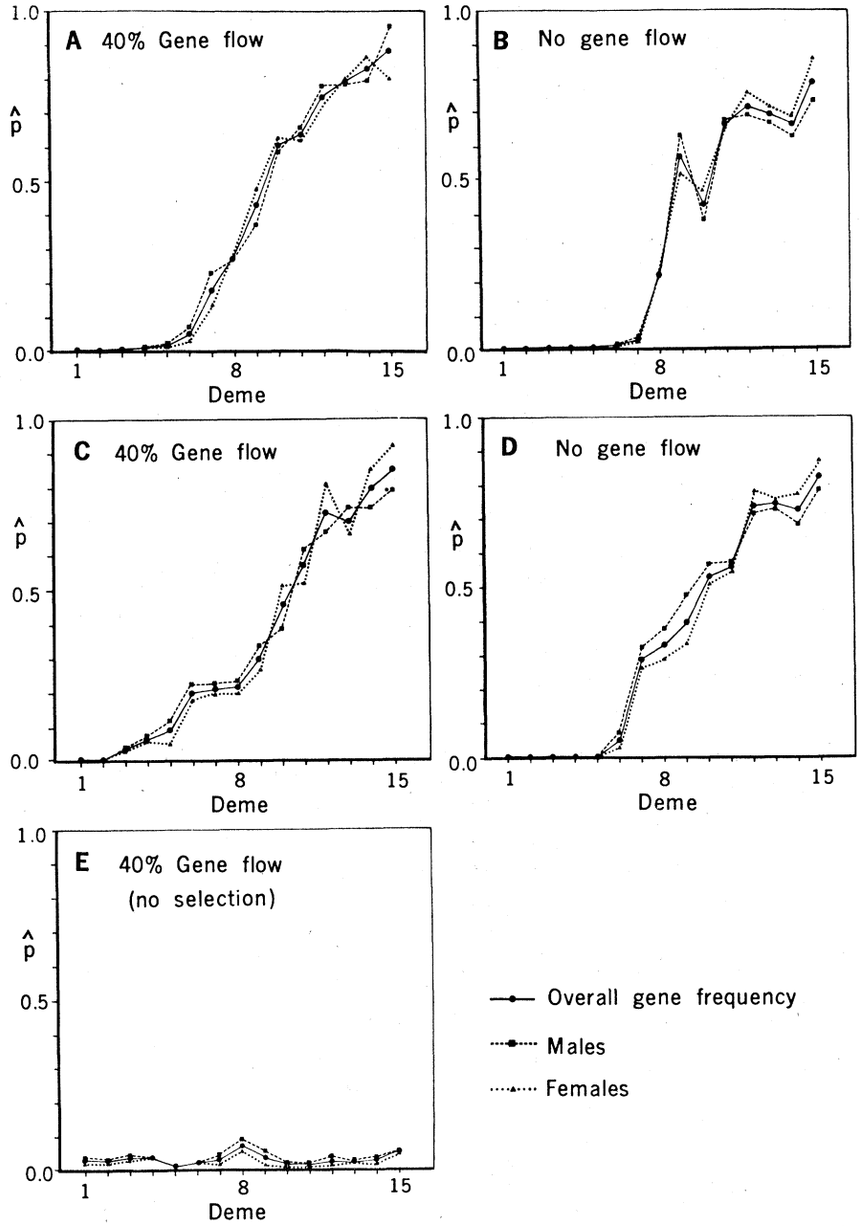

Fig. 1. The experimental clines (of *Drosophila*) showing *Bar* gene frequencies, $\hat{p}$, at generation 35. Generations 20 through 34 differ from 35 only in details. Demes 1 through 6 reached fixation for the "normal" gene within the first few generations as a result of the strong natural selection against *Bar*. These demes became polymorphic again in subsequent generations as a result of gene flow from demes 7 and above in sets A and C, and remained monomorphic in sets B and D with no gene flow. Replicates of demes 6 in sets B and D were subject to one generation of gene flow as in sets A and C during generation 15, and subsequently remained at a low *Bar* frequency. The four selective clines (A through D) are very similar, the fifth, set E, shows no sign of a cline.

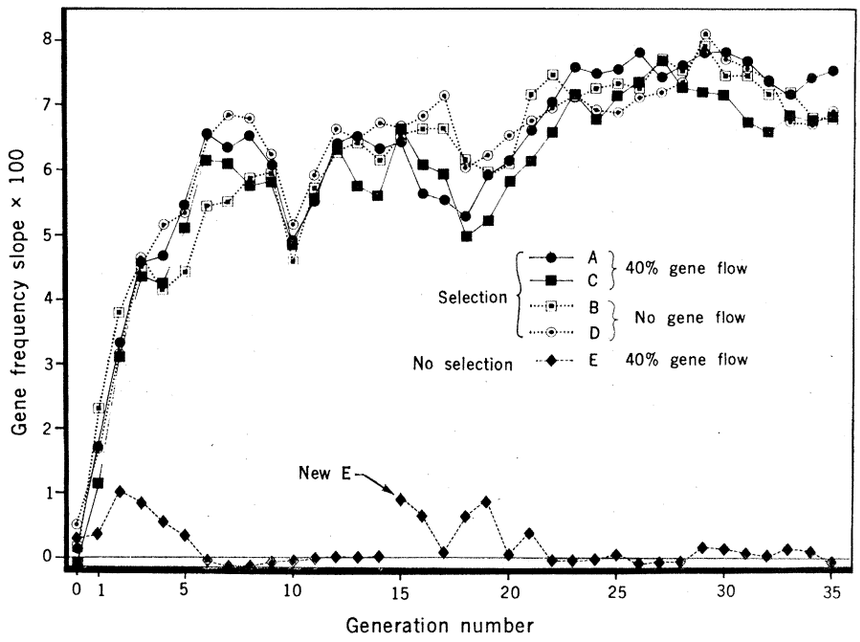

Fig. 2. The slopes of the experimental clines in each generation. The four selective clines remained very similar throughout the experiment; the effect of gene flow is not apparent. The fifth (set E) was reconstituted in generation 15 because almost all of its demes had reached fixation for the "normal" gene by generation 14. Set E was significantly different from zero slope only during generation 4.

two genotypes decreased at different rates along the same transect. This is probably one of the most realistic models. Special cases have been considered mathematically by both Fisher and Kimura (*8*) and by Slatkin (*14*).

The *heterozygous advantage model*, 2, is similar to that of many other authors (*31*). In this model the probabilities of survival of the homozygotes form selection gradients, but the heterozygote has a spatially constant fitness which is always greater than either homozygote by a minimum amount h_1 (see Fig. 3b).

A modification of model 2 is the *local heterozygous advantage model*, 3, in which the heterozygotes' survival is also position-dependent, and always a fixed amount, h_2, greater than either homozygote in the same deme (see Fig. 3c).

In the *frequency-dependent model*, 4, the probability of survival of each genotype in a deme in location x is related to its frequency in the same deme by:

$$W_i(x) = 1 - s\,[U_i - f_i(x)]$$

where U_i is the frequency of the ith genotype whose "focal frequency," $f_i(x)$, depends upon the genotype's position, x, in the deme series, and s is the strength of selection. The focal frequency is the optimum genotype frequency for a given deme, or the genotype frequency at which the probability of that genotype's survival is maximized (*32*) (see Fig. 3d).

Deterministic and Monte Carlo simulations of each model were executed on an ICL 4-75 computer, a wide variety of selection and gene flow parameters being used. Because the Monte Carlo simulations did not differ significantly from the deterministic runs, I will discuss only the latter. The deterministic simulations consisted of $d = 50$ demes of $N = 50$ pairs each (similar results were obtained for other values of d and N). Figure 3 indicates the kinds of selection gradients used in the simulations shown in Figs. 4 and 5. Figures 4 and 5 indicate the A gene frequencies, $\hat{p}$, at equilibrium, and the equilibrium slopes of the clines produced by various magnitudes of gene flow (g), and selection strengths in each model. The equilibrium slope is the regression of gene frequency [transformed into angles (*33*)] on deme number, calculated in the central third of the series to minimize edge effects.

Equilibrium Configurations of the Models

The gradient model produces a cline with a very marked local steepening in the vicinity of the null point for all but the very weakest selection gradients (Figs. 4a and 5a). The greatest effect on slope is found at low levels of gene flow coupled with weak selection gradients. As the slope of the selection gradient (I) increases the attenuation of

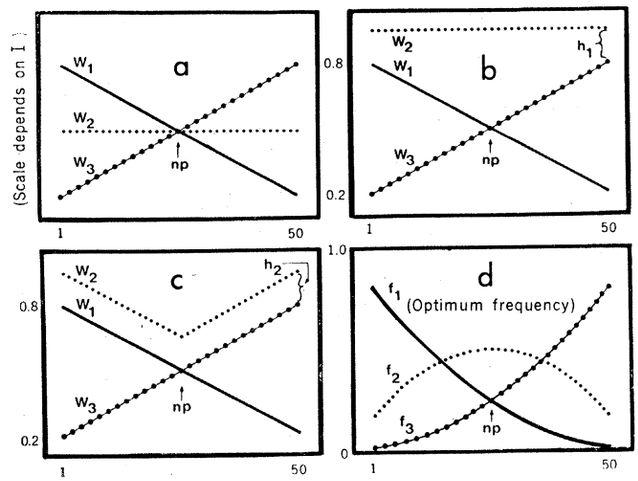

Fig. 3. The modes of selection in the four models shown in Figs. 4 to 6. (a) Gradient model; (b) heterozygous advantage model; (c) local heterozygous advantage model; (d) frequency-dependent model. In (a) through (d) the horizontal axis is the position in the deme series. In (a) through (c) the vertical axis is the absolute survival value for each genotype; W_1 for AA, W_2 for Aa, and W_3 for aa. In (d) the vertical axis is the optimum frequency or focal frequency, f, for each genotype at each deme; any deviation from these frequencies at a given position in the deme series, and the selection against the genotype, increases (see text); *np* is the null point; I is the increment in selection between adjacent demes; h_1 is the minimum amount by which the spatially constant fitness of the heterozygote is always greater than that of either homozygote; h_2 is the fixed amount by which the fitness of the heterozygote is always greater than the fitness of either of the homozygotes in the same deme.

slope due to dispersal along the cline is progressively reduced (Fig. 5a). For very weak gradients the differentiation may be very sharp, even for 100 percent gene flow ($g = 1.0$ in Fig. 4a). It should be emphasized that in this and the other models there is no sharp environmental change (Fig. 3).

The heterozygous advantage model produces a roughly linear cline (Fig. 4b) as pointed out by Clarke (*31*). For a given selection gradient there is negligible change of slope for increased dispersal (Fig. 5b). Gene flow has a slightly greater effect when the cline (in the absence of gene flow) is nearly flat (not illustrated). Random fluctuations in a natural cline following this model would probably obscure changes due to dispersal.

The local heterozygous advantage model produces a cline with a local steepening in the vicinity of the null point (Fig. 4c) as in the gradient model. For small values of local heterosis, h_2, this model approaches model 1 (gradient) in the clines which it produces. As a result of the local steepening, the smoothing effect of gene flow is more apparent than in model 2, especially for weak selection (h_2 in Fig. 5c), but the clines produced are nearly as insensitive to the effects of gene flow as are the clines in model 1. Like the gradient model, most of the attenuating effect of gene flow takes place for changes in small values ($0 < g < 0.3$), and progressively decreases for the same changes around large values of g. However, for very large amounts of gene flow there is still a marked local steepening (Figs. 4c and 5c).

The frequency-dependent model with distance-dependent focal frequencies (f_1, f_2, and f_3 in Fig. 3d) produces a roughly linear cline if the focal frequencies are arranged as in the Hardy-Weinberg ratios for a linearly increasing series of gene frequencies (Figs. 3d and 4d). For moderate to strong selection strengths ($s > 0.1$) the effect of gene flow is very small, but for very weak selection ($s < 0.1$) the cline may become noticeably flattened for large magnitudes of gene flow (Fig. 5d).

Dispersal is not always random or nondirectional (*22–24, 28, 34*). The process of gene flow may be divided into a nondirectional and a directional component, spatial drift (*35*). To explore the effect that a biasing environmental factor, such as wind or stream flow, may have on a cline, an asymmetry (sy) was introduced into the models. A fraction $sy \cdot g$ emigrate to the deme on the left and a fraction $(1-sy) \cdot g$ emigrate to the deme on the right of the parental deme, where g is the total fraction of moving individuals as before, and sy is a coefficient of asymmetry between 0 and 1. In the previous models and in the experiment, $sy = 0.50$, and asymmetrical gene flow is obtained by varying the parameter sy from 0.50.

Figure 6 illustrates the effect of symmetrical and several degrees of asymmetry on the gradient and heterozygous advantage models. The results for models 3 and 4 are very similar to models 1 and 2, respectively. For a given asymmetry of gene flow (sy), the entire cline is shifted in the direction of the dispersal bias in proportion to the given degree of total gene flow (g). A greater asymmetry (sy more different from 0.50) will result in an increased shifting effect for each dispersal value (g), but has little effect on the slope of the cline. Thus an asymmetry in gene flow may shift the geographic location of a cline between differentiated areas without affecting the extent of the differentiation.

Discussion

Different geographic conditions may cause differing patterns of selection which nevertheless result in very similar cline structures (Figs. 3 and 4). In addition, a given geographic pattern of selection may produce different clinal shapes under differing conditions of dominance of the characters selected, and the type and amount of gene flow (Figs. 4 and 6) (*26*). It is therefore very important that a particular model should not be applied indiscriminately to a given natural cline without specific knowledge of the actual geography of natural selection and gene flow. There is no easy way to explain geographic differentiation.

Ehrlich and Raven (*10*) cite many examples of animals and plants which

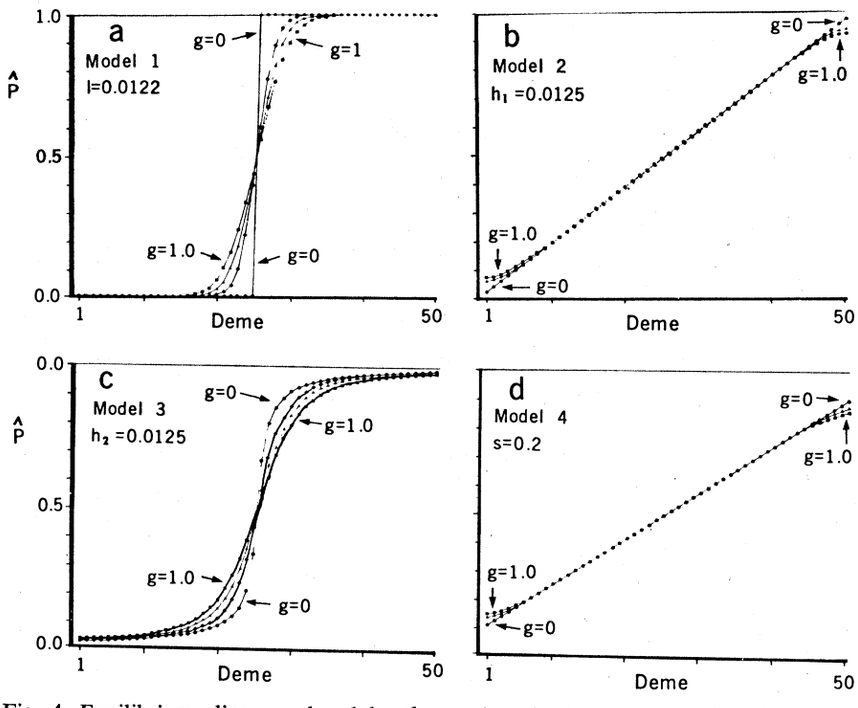

Fig. 4. Equilibrium clines produced by the modes of selection shown in Fig. 3 and various levels of gene flow. (a) Gradient model; (b) heterozygous advantage model; (c) local heterozygous advantage model; (d) frequency-dependent model. The horizontal axis is the position in the deme series and the vertical axis is the A gene frequency, $\hat{p}$, at equilibrium for various levels of gene flow from $g = 0.0$ to $g = 1.00$. A gene flow of 100 percent means that 100 percent of a given deme's population consists of immigrants after gene flow in each generation. In comparison with other experiments (*12*) where 50 percent is the maximum rate of gene flow, 100 percent is possible because there are more than two demes participating in gene flow. The clines produced by models 1 and 3 are very similar, as are the clines produced by models 2 and 4. The local steepening in models 1 and 3 have formed in the absence of sharp environmental changes in selection. All four models show excellent resistance to the attenuating effects of gene flow.

Table 3. The "swamping" effect of gene flow in relation to soil color but not to habitat. *N*, is sample size. [From Blair (*36*)]

Locality	Soil color	Habitat	Gene frequency	*N*
3 Miles N. Tularosa	Dark red	Grassy washes	0.567 ± 0.038	108
3 Miles S. Alamogordo	Pinkish gray	Mesquite	.248 ± .024	179
Salinas	Pinkish gray	Grassy	.545 ± .051	55
Lone Butte	Pinkish gray	Mesquite	.365 ± .046	57
White Sands	Creamy white	Gypsum dunes	.241 ± .086	13

have spatially differentiated, apparently in the absence of extensive barriers. They suggest that in most species gene flow is considerably more localized than is commonly thought (*10, 22–24*), and that it will probably prove to be the exception rather than the rule to find species with large amounts of gene flow and little differentiation. This is largely a matter of the difference between gene flow and true dispersal; gene flow requires a period of establishment of the new types into the new demes in addition to their reaching the new areas. There is some evidence that dispersing animals may find it difficult to become established if they move far from their birthplace (*22–24*). Mayr (*1*) and others, however, arguing for the de-differentiating effect of gene flow, cite many examples of spatial differentiation in which gene flow seems to have a marked effect.

One of the more commonly cited examples of the "swamping" effect of gene flow, Blair's study of *Peromyscus maniculatus* (*36*), needs reexamination. In the original paper he not only lists the soil colors and the estimated *gray* gene frequencies, but also the habitat types (see Table 3). Although the estimated *gray* gene frequencies do not correlate with soil color, they correlate very well with the habitat, indicating that gene flow is at least not preventing response to habitat type.

The relative magnitude of selection and gene flow alters the extent to which a given deme's gene frequency is influenced by that of its neighbors (*6, 14, 15, 27, 37*) (Figs. 4 and 5). For example, in one of Thoday's experiments (*12*), although g was 0.50, selection was of the order of 99 percent and differentiation (in this case response to disruptive selection) took place. Similarly, weak selection and strong gene flow is one of Jain and Bradshaw's simulations (*15*) produced poor local differentiation.

It is, however, an oversimplification to state that it is only the relative magnitude of gene flow and selection which affects the steepness of clines; this ignores the effects of spatial patterns of selection and gene flow. In most natural situations individuals are found grouped in favorable habitat patches connected as a network by dispersing individuals (*22–24, 28, 38*). Similarly, environmental factors such as temperature do not exist in two spatial states, but are often found in gradients (*24, 28*). A given deme with a given gene frequency may be subject to gene flow from other demes with higher gene frequencies, still others with lower gene frequencies, as well as from demes with roughly the same gene frequencies. If dispersal is relatively uniform among demes situated on a smooth environmental gradient, the net effect of gene flow will be small in each generation because the increasing effect on gene frequency by gene flow from the demes higher up on the gradient will be counteracted by gene flow from the demes lower down. In terms of Wright's formula (*5*), the mean gene frequency of the immigrants will not differ from the gene frequency of the deme receiving the immigrants on a smooth cline. This neutralizing effect will be effective for all levels of gene flow, hence clines resulting from smooth environmental gradients will be rather insensitive to the attenuating effects of gene flow, as shown by the experimental clines in *Drosophila* and the four models (Figs. 1 through 6). It is therefore possible for local differentiation, even marked differentiation, to occur along a relatively weak environmental gradient; for example, it is possible for differentiation to occur given a difference of $I = 0.008$ between adjacent demes as in Fig. 5a, an amount that might be difficult to measure in the field.

The self-canceling effect of gene flow along an environmental gradient is reduced if there is a rapid spatial change in selection or a large change in slope of the selection gradients causing the cline. This is because, in general, such

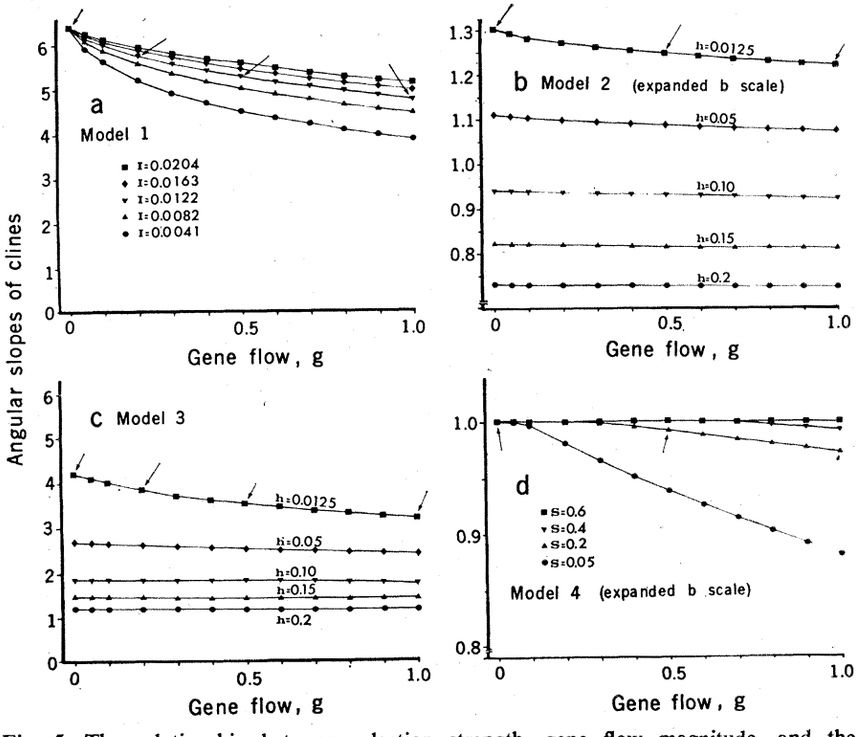

Fig. 5. The relationship between selection strength, gene flow magnitude, and the equilibrium slope of the clines for each model; (a) through (d) as in Fig. 4. The horizontal axis represents the magnitude of gene flow, g. The vertical axis represents the slopes of the clines (see text) at equilibrium. Note the expanded scales in (b) and (d), which are necessary to show any effects of gene flow in models 2 and 4. The parameter I is the strength of the selection gradient, or the difference in selection between adjacent demes; h_1 and h_2 are the strengths of heterosis (see Fig. 3) and s is the strength of frequency-dependence (see text). Arrows mark the slopes of the clines shown in Fig. 4, for comparison. The amount of heterosis (h_1 or h_2) affects the slope of clines more than any differences in gene flow in models 2 and 3. In all four models gene flow has a small effect.

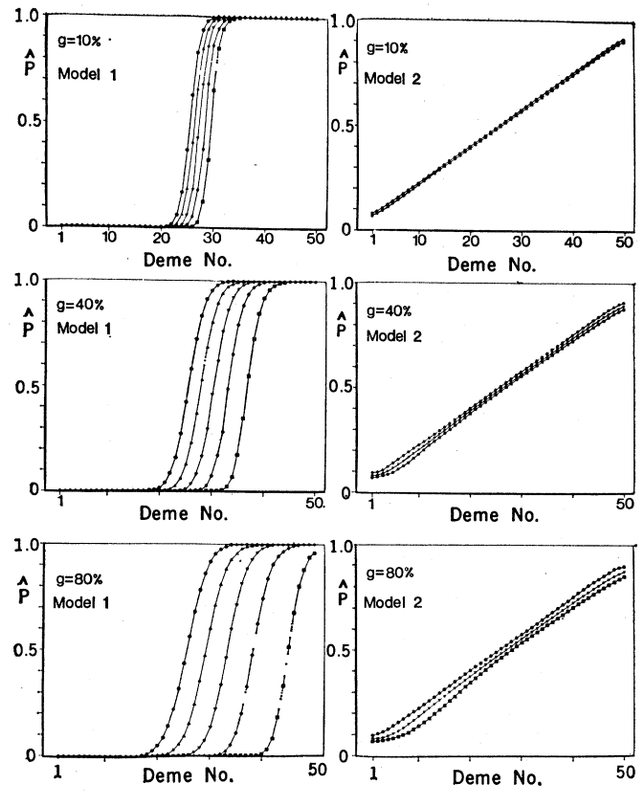

Fig. 6. The effect of an asymmetry in gene flow on the equilibrium clines of models 1 and 2. Horizontal axes represent the positions on the deme series, and the vertical axes represent the equilibrium gene frequencies as in Fig. 4. The three graphs on the left illustrate the effect of three different levels of gene flow, g, on the gradient model, and the three graphs on the right illustrate the same effect for the heterozygous advantage model. In each graph the equilibrium clines for several levels of asymmetry (sy) as well as for completely symmetrical gene flow ($sy = 0.50$) are shown for comparison. For model 1, from left to right, $sy = 0.50$, 0.40, 0.30, 0.20, and 0.10. For model 2 (three graphs on the right), from left to right, $sy = 0.50$, 0.30, 0.10. A greater amount of gene flow (g) makes the system more sensitive to the effects of a given asymmetry of gene flow, and a greater asymmetry (sy different from 0.50) results in a greater shifting of the cline for a given amount of gene flow (g). Model 1 is more sensitive to the shifting effect of asymmetrical gene flow than is model 2, but in both models the steepness of the cline is not noticeably affected by the asymmetry.

conditions increase the difference between the mean gene frequency of the immigrants from the adjacent demes and the gene frequency of the deme receiving the immigrants (*15*), as apparently found in studies of *Peromyscus* (*39*) and *Pachycephala* (*40*). The effect of gene flow may also be noticeable at the ends of a series of demes, and is a form of edge effect (Fig. 4, b and d). If there are very few demes in a cline the effect of gene flow will be very much greater. The greatest possible effect of gene flow is found in the two-deme model (*12, 13, 37*) because there can be no canceling of the effects of gene flow from areas characterized by high and low gene frequencies. Theoretical conclusions from the two-deme model are thus not applicable to species distributed among more than two demes connected by gene flow. With only a few demes the effect of gene flow may also be obvious. In Jain and Bradshaw's simulations with asymmetrical gene flow (*15*) among ten demes, the asymmetry caused a piling up of the dispersing genes at the edge of the series, greatly reducing the sharpness of the differentiation. The cline had been, in effect, shifted off the edge of the deme series. In the models discussed here ($d = 50$ demes, Fig. 6), the edge of the deme series is too far away from the null point to have any appreciable effect, except for extremely asymmetrical gene flow ($sy = 0.10$). In general, provided that differences in selection between adjacent demes (I) remain roughly similar, the canceling effect of equidistant but oppositely situated demes will buffer clines against the attenuating effect of gene flow.

Conclusions

There are many possible spatial patterns of selection and gene flow that can produce a given cline structure; the actual geography of natural selection and gene flow must be worked out before an attempt is made to explain a given natural cline in terms of a model.

The results of experimental and theoretical models show that it is possible for local differentiation to evolve parapatrically in spite of considerable gene flow if the selection gradients are relatively uniform. Irregularities in environmental gradients increase the sensitivity of clines to the effects of gene flow in proportion to the increase in the differences in gene frequencies between the emigrants and the demes receiving the immigrants. It is not necessary for a sharp spatial environmental change to be present for distinct differentiation to occur. In some cases even a gentle environmental gradient can give rise to marked spatial differentiation along a genetically continuous series of demes; such environmental differences may be below the practical limits of resolution in field studies. Any asymmetry in gene flow does not lead to dedifferentiation if the environmental gradient is smooth; it merely shifts the position of the transition zone between the differentiated areas from that which would be expected if there were no asymmetry. Abrupt geographic differences in gene, genotype, or morph frequencies should not, therefore, be interpreted as evidence for environmental changes in the immediate vicinity of the steepest part of the cline; neither should they be interpreted as evidence for geographic barriers, sharp environmental differences, or sexual isolation among the differentiated groups of populations when there are no other sources of evidence for these phenomena. Gene flow may be unimportant in the differentiation of populations along environmental gradients.

References and Notes

1. E. Mayr, *Amer. Natur.* **74**, 249 (1940); *Systematics and the Origin of Species from the Viewpoint of a Zoologist* (Columbia Univ. Press, New York, 1942); *Animal Species and Evolution* (Harvard Univ. Belknap Press, Cambridge, 1963).
2. Th. Dobzhansky, *Genetics and the Origin of Species* (Columbia Univ. Press, New York, 1970).
3. ———, *Amer. Natur.* **74**, 312 (1940); H. M. Smith, *Biologist Phi Sigma Soc.* **49**, 43 (1967).
4. G. G. Simpson, *The Major Features of Evolution* (Columbia Univ. Press, New York, 1953); P. J. Darlington, Jr., *Zoogeography:*

The Geographical Distribution of Animals (Wiley, New York, 1957); B. Rensch, *Evolution Above the Species Level* (Methuen, London, 1959); V. Grant, *The Origin of Adaptations* (Columbia Univ. Press, New York, 1963).
5. S. Wright, *Genetics* **16**, 97 (1931).
6. ———, *ibid.* **28**, 114 (1943); *ibid.* **31**, 39 (1946); *Evolution and the Genetics of Populations*, vol. 2, *The Theory of Gene Frequencies* (Univ. of Chicago Press, Chicago, 1969); F. J. Rohlf and G. D. Schnell, *Amer. Natur.* **105**, 295 (1971).
7. J. B. S. Haldane, *J. Genet.* **48**, 277 (1948).
8. R. A. Fisher, *Biometrics* **6**, 353 (1950); M. Kimura, *Annu. Rep. Nat. Inst. Genet. Mishima-City, Japan* **9**, 84 (1958).
9. M. Kimura and G. H. Weiss, *Genetics* **49**, 561 (1964); M. Kimura and T. Maruyama, *Genet. Res.* **18**, 125 (1971).
10. P. R. Ehrlich and P. H. Raven, *Science* **165**, 1228 (1969).
11. For example, J. Maynard-Smith, *Amer. Natur.* **100**, 637 (1966).
12. J. M. Thoday, *Nature* **181**, 1124 (1958); ——— and T. B. Boam, *Heredity* **13**, 204 (1959); E. Millicent and J. M. Thoday, *ibid.* **16**, 219 (1961); J. M. Thoday and J. B. Gibson, *Amer. Natur.* **105**, 86 (1971).
13. F. A. Streams and D. Pimentel, *ibid.* **95**, 201 (1961); Th. Dobzhansky and B. Spassky, *Proc. Roy. Soc. London Ser. B.* **168**, 27 (1967); ———, J. Sved, *ibid.* **173**, 191 (1969); Th. Dobzhansky, H. Levene, B. Spassky, *ibid.* **180**, 21 (1972).
14. M. Slatkin, thesis, Harvard University (1971).
15. S. K. Jain and A. D. Bradshaw, *Heredity* **21**, 407 (1966).
16. Parapatric divergence is divergence between adjacent but genetically continuous populations. H. M. Smith, *Syst. Zool.* **14**, 57 (19(*ibid.* **18**, 254 (1969); M. J. D. White, R. E. Blackith, R. M. Blackith, J. Cheney, *Aust. J. Zool.* **15**, 263 (1967); M. J. D. White, *Science* **159**, 1065 (196 K. H. L. Key, *Syst. Zool.* **17**, 14 (1968).
17. J. S. Huxley, *Nature* **142**, 219 (1938); *Bijdr. Dierk. Leiden* **27**, 491 (1939).
18. F. B. Sumner, *Bibliogr. Genet.* **9**, 1 (1932).
19. F. Salomonsen, *Dan. Biol. Medd.* **22**, 1 (1955).
20. E. B. Ford, *Biol. Rev. Cambridge Phil. Soc.* **20**, 73 (1945).
21. Examples of morph-ratio clines include: H. B. D. Kettlewell and R. J. Berry, *Heredity* **16**, 403 (1961); *ibid.* **24**, 1 (1969); H. B. D. Kettlewell, R. J. Berry, C. J. Cadbury, G. C. Phillips, *ibid.*, p. 15; H. N. Southern, *J. Zool. London Ser. A* **138**, 455 (1966); A. J. Cain and J. D. Currey, *Phil. Trans. Roy. Soc. London Ser. B.* **246**, 1 (1962); A. P. Platt and L. P. Brower, *Evolution* **22**, 699 (1968); O. Halkka and E. Mikkola, *Hereditas* **54**, 140 (1965); B. C. Clarke, in *Evolution and Environment*, E. T. Drake, Ed. (Yale Univ. Press, New Haven, 1968), p. 351; B. C. Clarke and J. J. Murray, in *Ecological Genetics and Evolution*, R. Greed, Ed. (Blackwells, Oxford, 1971), p. 51; J. A. Bishop and P. S. Harper, *Heredity* **25**, 449 (1969); J. A. Bishop, *J. Anim. Ecol.* **41**, 209 (1972); G. Hewitt and F. M. Brown, *Heredity* **25**, 365 (1970); G. Hewitt and C. Ruscoe, *J. Anim. Ecol.* **40**, 753 (1971); H. Wolda, *ibid.* **38**, 623 (1969); F. B. Livingstone, *Amer. J. Phys. Anthropol.* **31**, 1 (1969).
22. C. P. Haskins, E. F. Haskins, J. J. A. McLaughlan, R. E. Hewitt, in *Vertebrate Speciation*, W. F. Blair, Ed. (Univ. of Texas Press, Austin, 1961), p. 320.
23. A. J. Bateman, *Heredity* **1**, 234, 303 (1947); *ibid.* **4**, 353 (19 R. N. Colwell, *Amer. J. Bot.* **38**, 511 (1951); M. R. Roberts and H. Lewis, *Evolution* **9**, 445 (1955); C. P. Haskins, personal communication; K. P. Lamb, E. Hassan, D. P. Scoter, *Ecology* **52**, 178 (1971). For localized distribution and problem of establishment see also: W. F. Blair, *Ann. N.Y. Acad. Sci.* **44**, 179 (1943); *Evolution* **4**, 253 (1950); L. R. Dice, *Amer. Natur.* **74**, 289 (1940); P. Labine, *Evolution* **20**, 580 (1966); H. Lewis, *ibid.* **7**, 1 (1953); W. Z. Lidicker, personal communication; J. T. Marshall, Jr., *Condor* **50**, 193, 233 (1948); R. K. Sealander, *Amer. Zool.* **10**, 53 (1970); P. Voipio, *Ann. Zool. Fenn.* **15**, 1 (1952); P. K. Anderson, *Science* **145**, 177 (1964).
24. N. W. Timofeeff-Ressovsky, in *The New Systematics*, J. S. Huxley, Ed. (Oxford Univ. Press, Oxford, 1940), p. 73.
25. The null point is the position at which selection changes over from favoring one type to favoring another.
26. J. A. Endler, in preparation.
27. L. M. Cook, *Coefficients of Natural Selection* (Hutchinson Univ. Library, Biological Sciences No. 153, London, 1971); F. B. Livingstone, *Amer. J. Phys. Anthropol.* **31**, 1 (1969).
28. W. C. Allee, A. E. Emerson, O. Park, T. Park, K. P. Schmidt, *Principles of Animal Ecology* (Saunders, Philadelphia, 1949); H. C. Andrewartha and L. C. Birch, *The Distribution and Abundance of Animals* (Univ. of Chicago Press, Chicago, 1954); G. L. Clarke, *Elements of Ecology* (Wiley, New York, 1954); R. Geiger, *The Climate Near the Ground* (translation, Harvard Univ. Press, Cambridge, 1966).
29. Results for autosomal and sex-linked systems do not differ for the models to be discussed, except that, for a given amount of selection, the sex-linked system is less sensitive to the effects of gene flow. This is because the effective gene selection on males in sex-linked loci makes the *net* selection stronger, compared to autosomal loci, for the population as a whole. See C. C. Li, *Population Genetics* (Univ. of Chicago Press, Chicago, 1955) for a good discussion of sex-linkage and selection.
30. The equilibrium configurations are not significantly altered if the emigrants from the end demes do not return, unless the number of demes (d) is very small (J. A. Endler, unpublished data).
31. See, for example, the models of B. C. Clarke [*Amer. Natur.* **100**, 389 (1966)] and those in (*14*).
32. This model incorporates Clarke's model of frequency-dependence; see B. C. Clarke, *Evolution* **18**, 364 (1964).
33. R. A. Fisher and F. Yates, *Statistical Tables for Biological, Agricultural, and Medical Research* (Oliver & Boyd, Edinburgh, 1948); R. R. Sokal and F. J. Rohlf, *Biometry* (Freeman, San Francisco, 1969).
34. See, for example, C. G. Johnson, *Migration and Dispersal of Insects by Flight* (Methuen, London, 1969); J. Antonovics, *Amer. Sci.* **59**, 593 (1971).
35. E. C. Pielou, *An Introduction to Mathematical Ecology* (Wiley-Interscience, New York, 1969).
36. W. F. Blair, *Contrib. Lab. Vertebrate Biol. Univ. Mich.* No. 36, 1 (1947).
37. P. A. Parsons, *Genetica* **33**, 184 (1963).
38. G. Hewitt and B. John, *Chromosoma* **21**, 140 (1967); *Evolution* **24**, 169 (1970); G. Hewitt, personal communication; H. Wolda, *J. Anim. Ecol.* **38**, 305, 623 (1969).
39. L. R. Dice, *Contrib. Lab. Vertebrate Genet. Univ. Mich.* No. 8 (1939), p. 1; *ibid.* No. 15 (1941), p. 1.
40. I. C. J. Galbraith, *Bull. Brit. Mus. Natur. Hist. Zool.* **4**, 133 (1956).
41. I am grateful to the National Science Foundation for a graduate fellowship in support of this study. I thank Prof. Alan Robertson and the Institute of Animal Genetics, University of Edinburgh, for the *Drosophila*, and for kindly providing me with fresh medium throughout the study. Criticism of the manuscript by Professors John Bonner and Jane Potter, Dr. Philip Ashmole, Peter Tuft, Dr. David Noakes, Dr. John Godfrey, Dr. Caryl P. Haskins, and M. C. Bathgate was very welcome. In particular, I thank my supervisor, Professor Bryan C. Clarke, for help and criticism throughout this study. Any errors or omissions are entirely my own. I thank the Edinburgh Regional Computing Center and the Edinburgh University Zoology Department for generous computer time allowances. I will supply the specially written IMP language program upon request.

On Being Sane in Insane Places

D. L. Rosenhan

If sanity and insanity exist, how shall we know them?

The question is neither capricious nor itself insane. However much we may be personally convinced that we can tell the normal from the abnormal, the evidence is simply not compelling. It is commonplace, for example, to read about murder trials wherein eminent psychiatrists for the defense are contradicted by equally eminent psychiatrists for the prosecution on the matter of the defendant's sanity. More generally, there are a great deal of conflicting data on the reliability, utility, and meaning of such terms as "sanity," "insanity," "mental illness," and "schizophrenia" (*1*). Finally, as early as 1934, Benedict suggested that normality and abnormality are not universal (*2*). What is viewed as normal in one culture may be seen as quite aberrant in another. Thus, notions of normality and abnormality may not be quite as accurate as people believe they are.

To raise questions regarding normality and abnormality is in no way to question the fact that some behaviors are deviant or odd. Murder is deviant. So, too, are hallucinations. Nor does raising such questions deny the existence of the personal anguish that is often associated with "mental illness." Anxiety and depression exist. Psychological suffering exists. But normality and abnormality, sanity and insanity, and the diagnoses that flow from them

The author is professor of psychology and law at Stanford University, Stanford, California 94305. Portions of these data were presented to colloquiums of the psychology departments at the University of California at Berkeley and at Santa Barbara; University of Arizona, Tucson; and Harvard University, Cambridge, Massachusetts.