

short lengths and "low twitch" values was strikingly apparent, as already reported for whole muscle (6). The same correlation was evident not only for twitches but also for tetanic force in the steady state. But the increased light emission was not correlated with the ratio of initial twitch to tetanus force. The unexceptionable association, therefore, was not among relative enhancement of intracellular Ca^{2+} transients, temperature, type of agent, or intrinsic twitch to tetanic force ratio. Cell length was the most consistent factor.

We conclude that these observations support and extend previous suggestions about the relative degree of activation in skeletal muscle allowed to shorten (2). Calcium-induced activation is progressively less than maximum at all muscle lengths shorter than those along the descending limb of the length-tension relation. In addition, the optimum length for twitch force is, by itself, neither an adequate means to assure that muscles are studied near the same average striation spacing nor is it, as the sole criterion, an adequate starting point to estimate the relative efficacy of the potentiating ability of an agent.

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19 May 1981

Intense Natural Selection in a Population of Darwin's Finches (Geospizinae) in the Galápagos

Abstract. *Survival of Darwin's finches through a drought on Daphne Major Island was nonrandom. Large birds, especially males with large beaks, survived best because they were able to crack the large and hard seeds that predominated in the drought. Selection intensities, calculated by O'Donald's method, are the highest yet recorded for a vertebrate population.*

There are few well-documented examples of natural selection causing avian populations to track a changing environmental phenotypically. This is partly because birds meet environmental challenges with remarkable behavioral and physiological flexibility (1), partly because birds have low reproductive rates and long generation times, and partly because it has been difficult for ecologists to quantify corresponding phenotypic and environmental changes in most field studies. In this report we demonstrate directional natural selection in a population of Darwin's finches and identify its main cause.

We studied Darwin's medium ground finch (*Geospiza fortis*) on the 40-ha islet of Daphne Major, the Galápagos, from July 1975 to June 1978. Each of more than 1500 birds was color-banded and measured for seven external morphological characters (2). Continuous records were kept of the banded birds and of rainfall. Each year during the breeding season (January to May) we banded nestlings and compiled nest histories. Three times a year (before, during, and after the breeding season) we collected the following data: (i) the number of seeds of each plant species in 50 randomly chosen 1.0-m² quadrats; (ii) a standardized visual census of finches over the entire island; and (iii) a minimum of 100 point records of feeding behavior, accumulated by noting food items eaten by banded birds encountered during non-systematic searches (2).

During the early 1970's Daphne Major received regular rainfall, resulting in large finch populations and food supplies (2). From December through June in 1976 and 1978 we recorded rainfalls of 127 and 137 mm, respectively—sufficient for abundant production of plants, insects, and finches. However, in 1977 only 24 mm of rain fell on Daphne Major during the wet season (3, 4). *Geospiza fortis* did not breed at all in 1977 and suffered an 85 percent decline in population (Fig. 1A). The decline was correlated with a reduction in seed abundance ($r = .86$, $P < .01$) (Fig. 1B). Seeds form the staple diet of *G. fortis*, particularly in the dry season, when other plant matter and insects are scarce (2).

Between June 1976 and March 1978, the mortality, and possibly emigration (5), of *G. fortis* was nonrandom with respect to age, sex, and phenotype. Only one of 388 *G. fortis* nestlings banded in 1976 survived to 1978, and while the sex ratio was roughly equal in 1976, it had become skewed to six males to one female in 1978. Most significantly, the birds surviving into 1978 were considerably larger than those that disappeared (Fig. 1C). We use principal component 1 (6) as an index of overall body size because here, as in other avian studies (7), it explains a substantial portion (67 percent) of the phenotypic variance in the *G. fortis* population and has consistently high, positive correlations with the morphological variables it summarizes. The change is most obvious in the plot including all birds because it incorporates the changing sex ratio (most of the morphological characters are 4 percent larger in males than in females) and perhaps a small age effect, although all birds less than 12 weeks old were excluded from the analysis.

Small seeds declined in abundance faster than large ones, resulting in a sharp increase in the average size and hardness of available seeds (Fig. 1D). There was a corresponding change in feeding behavior. In May 1976 only 17 percent of feeding was on medium or large seeds [size-hardness index $\sqrt{DH} \geq 1.0$ (8)], while in May 1977 49 percent of feeding was on such seeds. During the present and related studies (2), large birds ate larger seeds than smaller birds, suggesting that small birds disappeared because they could not find enough food. For example, in a quantitative test of size-related feeding behavior, 198 birds that were only recorded eating seeds with a size-hardness index < 1.0 were significantly smaller than another 121 birds that routinely ate seeds with size-hardness indices ranging from 1.0 to 8.7 (8). In 1977, during the normally lush wet season, larger birds fed heavily on seeds extracted from the large, hard mericarps of *Tribulus cistoides* ($\sqrt{DH} = 8.68$), a food item ignored by almost all birds in earlier years (2). Many finches failed to molt that year, and their condition gradually deteriorated. Small

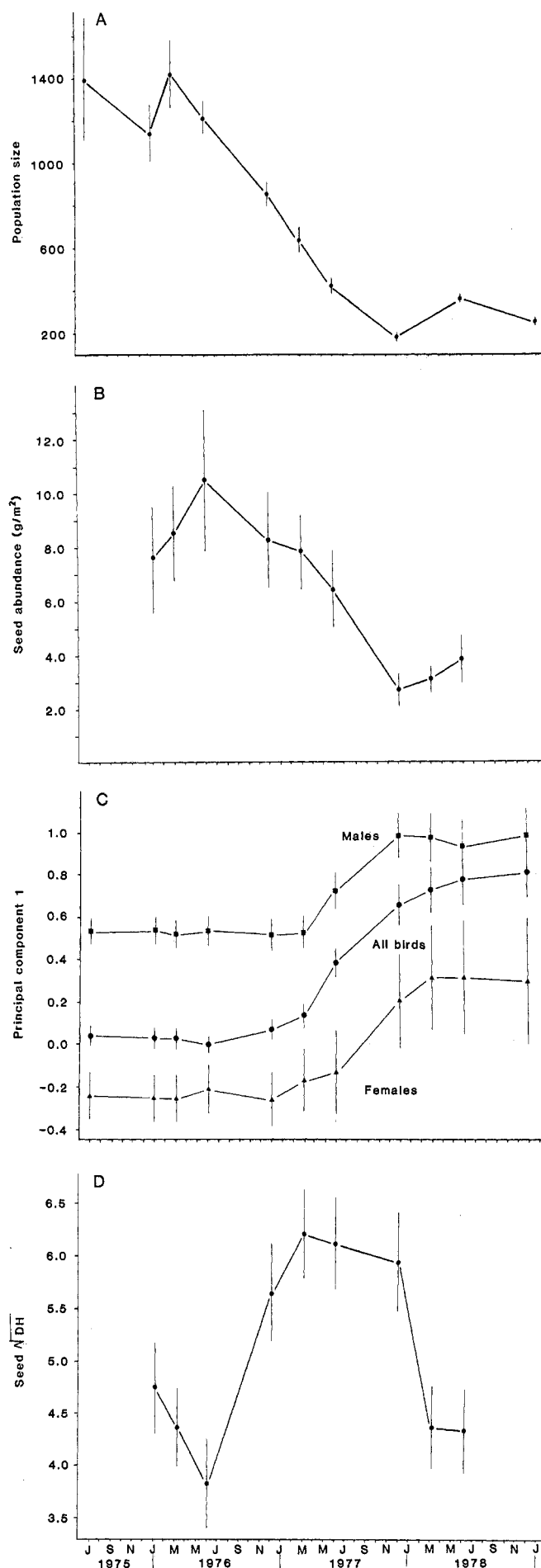
birds fed heavily on *Chamaesyce* spp., the only producer of small seeds in 1977, and as a result their plumage often became matted with the latex of this euphorb. Several dead birds were found with completely bald heads from feeding on *Chamaesyce* and from digging in the soil for seeds. Such plumage loss may have led to increased energy loss during the cool nights of the dry season. The dependence of the finches on a declining seed supply ceased at the end of 1977, when *Opuntia* cactus began flowering and all birds fed heavily on its pollen and nectar (2).

It is reasonable to infer natural selection from the greater survival of large birds because about 76 percent of the variation in the seven morphological measurements and in principal component 1 scores is heritable (3, 9). To calculate the intensity of selection we use O'Donald's method (10), $\Delta\bar{w}/\bar{w} = (\bar{w} \text{ before selection} - \bar{w} \text{ after selection})/\bar{w} \text{ before selection} = V_w/\bar{w}^2$, where $\Delta\bar{w}/\bar{w}$ estimates the proportional increase in mean fitness of the population as a result of selection and V_w is the variance in fitness. O'Donald provides several functions relating fitness to phenotypic characters and gives formulas for calculating $\Delta\bar{w}/\bar{w}$ from the four moments of phenotypic distributions before and after selection.

Table 1 summarizes the phenotypic changes in the *G. fortis* population between June 1976 and January 1978. Changes in variance were small and none was statistically significant (11). Changes in means of most characters were significant and in the direction expected if larger birds survived best (12). A thorough examination of the data with both univariate and multivariate techniques suggests that the main differences between birds that survived and those that did not were in body size and bill dimensions, particularly bill depth (8). Table 1 includes standardized coefficients that show the relative contributions of each character to the discriminant functions separating survivors and nonsurvivors. Our analysis includes only adult finches measured before the 1976 dry season; the 1978 survivors are a subset of those 1976 individuals, and thus the 1978 range for any given variable falls entirely within the corresponding 1976 range.

Because selection acted primarily on character means, we assume a linear fitness function (10). The highest values for $\Delta\bar{w}/\bar{w}$ are observed in the discriminant functions and in variables weighted heavily by the functions (Table 1). Several of the selection intensities are considerably greater than any published to

Fig. 1. Temporal changes in finch numbers, seed abundance, morphology, and average seed size on Daphne Major. (A) Population estimates (means \pm 95 percent confidence limits) derived from a Lincoln index based on regular visual censuses of a marked population. (B) Estimates of seed abundance [means \pm standard errors (S.E.)], excluding two seed species never eaten by any Galápagos finches. (C) Principal component 1 scores (means \pm S.E.) for birds alive in each sample period, with coefficients calculated from the combined sample of all birds measured. (D) Estimates of the average \sqrt{DH} index (means \pm S.E.) of edible seeds available in each study period (8).



date. For example, O'Donald (10) reanalyzed H. Bumpus's data on the survival of house sparrows (*Passer domesticus*) during a particularly severe winter storm, and concluded that such values as the $\Delta\bar{w}/\bar{w} = .255$ he obtained for the change in discriminant score between the before-storm and after-storm sparrow samples indicated selection "more intense than any which has since been observed acting on particular quantitative characters" (10).

Table 1 and Fig. 1 show that females experienced stronger selective mortality than males, in agreement with the evidence that the sex ratio became skewed in favor of males. There is no question that the overall effect of selection in the two sexes was similar: larger individuals survived best. There is some evidence that slightly different aspects of "largeness" were favored in males over females (13). The results for the combined population illustrate how a large phenotypic shift can occur both as the result of changes in the frequency of discrete classes of individuals (males and females) and in the average measurements of individuals within those classes.

Our data provide a link between a specific environmental factor (size of

available food) and phenotypic tracking of the environment. Others have consistently encountered difficulty in identifying the relation between complex and often rather small changes in body size and shape and general environmental parameters, such as temperature (14). Because of the high correlations between the seven characters we examined, it is difficult to specify the precise target of selection; univariate selection intensities and discriminant coefficients presented in Table 1 and calculated in the similar analyses of separate male and female groups (13) suggest that weight and bill dimensions are most important. In addition to the relation between bill morphology and changes in the food supply, it is likely that there were additional indirect selection pressures operating on, for example, body size for reasons associated with energetics (15) and dominance behavior (16). Furthermore, it is likely that a different set of selection pressures operates when food is abundant and population size is increasing, thus giving rise to oscillating directional selection (2).

Our results are consistent with the growing opinion among evolutionary ecologists that the trajectory of even well-buffered vertebrate species is large-

ly determined by occasional "bottle-necks" of intense selection during a small portion of their history (17). More specifically, given the many small, isolated, relatively sedentary, and morphologically variable populations of Darwin's finches (18, 19) and the high spatial (2, 19) and temporal (4) variability of the Galápagos, this type of event provides a mechanism for rapid morphological evolution. Occasional strong selection of heritable characters in a variable environment may be one of the keys to explaining the apparently rapid adaptive radiation of the Geospizinae in the Galápagos (18, 20).

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6. Principal components were extracted from the covariance matrix of the seven log-transformed variables, with all birds combined. The first component explained 67 percent of the total variance and had large correlations with the seven original variables; following the sequence used in Table 1, these component-character correlations were .88, .67, .60, .85, .94, .93, and -.49. Component 2 explained a further 16 percent of the variance and was strongly correlated with bill length at a depth of 4 mm ($r = .87$), followed by bill length ($r = .30$), with other characters showing low correlations of mixed signs. Correlations with length at a depth of 4 mm are reversed because this character is necessarily smaller in larger birds. Other analyses with these finches confirm that principal components 1 and 2 usually reflect overall body size and bill "pointedness," respectively, whether based on covariance or correlation matrices.
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8. The size-hardness index is the geometric mean of the depth (D) of a seed species in millimeters and its hardness (H) in newtons. In Fig. 1D, average \sqrt{DH} values are obtained by weighting the mean number of seeds (of each species) per square meter by the average seed mass and \sqrt{DH} for that species (2). The tests of hard-

Table 1. Characteristics of finches surviving the 1977 drought. The sample measured before selection includes all mature *G. fortis* measured up to the end of May 1976. The sample measured after selection is the subset of the first sample still present on Daphne Major in March 1978. Standardized discriminant function coefficients (SDFC's) reflect the relative contribution of each univariate character to the discriminant function separating survivors and nonsurvivors. Principal component 1 is an index of body size and principal component 2 reflects bill pointedness: both are presented as standardized variables (7). Separate discriminant functions (11) were used to distinguish between survivors and nonsurvivors in the combined sample of birds emphasized here and in smaller samples of males only and females only, for which the discriminant and principal component scores alone are given here. The mean discriminant scores are unstandardized and, because different functions were used, scores of the three groups are not comparable. Values for $\Delta\bar{w}/\bar{w}$ give the proportionate increase in mean fitness as a result of selection, assuming a linear fitness function (10).

Variable	Sample size		Means		Variances		SDFC	$\Delta\bar{w}/\bar{w}$
	Before	After	Before	After	Before	After		
<i>All birds</i>								
Weight (g)	642	85	15.79	16.85	2.37	2.43	0.45	.49
Wing chord (mm)	642	85	67.71	69.22	5.89	5.01	0.35	.39
Tarsus length (mm)	642	85	18.76	19.11	0.57	0.49	0.13	.22
Bill length (mm)	641	85	10.68	11.07	0.55	0.57	0.14	.23
Bill depth (mm)	642	85	9.42	9.96	0.68	0.66	0.45	.44
Bill width (mm)	641	85	8.68	9.01	0.36	0.34	-0.56	.31
Bill length at depth of 4 mm	642	85	3.55	3.41	0.08	0.08	-0.35	.24
Principal component 1	640	85	0.00	0.73	1.06	0.95		.50
Principal component 2	640	85	0.01	-0.13	0.97	0.99		.02
Discriminant function	640	85	-11.55	-12.41	1.13	0.99		.66
<i>Males only</i>								
Principal component 1	198	56	0.54	0.98	0.92	0.76		.21
Discriminant function	198	56	7.35	6.87	0.75	0.64		.31
<i>Females only</i>								
Principal component 1	66	15	-0.21	0.32	0.97	0.96		.28
Discrimination function	66	15	-2.77	-3.71	1.57	1.81		.57

versus soft-seed feeders consisted of univariate *t*-tests on all seven morphological variables; in all cases birds feeding on large seeds were significantly larger ($P < .0001$) than those feeding only on small seeds. The seven-variable multivariate analysis of variance between the two groups was also highly significant [$F(7,311) = 7.94, P < .0001$]. The standardized coefficients of the discriminant function separating the two feeding groups weighted bill depth most heavily (.80), followed by wing chord (.57), with all other variables having coefficients under .25. This underlines the link between bill depth and feeding behavior, which persisted among the survivors at the end of 1977 (P. R. Grant, *Anim. Behav.* in press).

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11. Separate linear discriminant functions were computed for males alone, for females alone, and for both combined with mature birds of uncertain sex, each maximizing the distance between the centroids of survivors and nonsurvivors in that group. Unstandardized discriminant scores were calculated for each bird by using the appropriate equation. The variances for the seven original variables, the first and second principal components, and the discriminant function of birds that survived from June 1976 to March 1978 were compared with those of birds that disappeared. The ten comparisons were made for males, for females, and for the combined group; in 21 of the 30 comparisons the selected group was less variable, but none of the 30 *F*-tests approached significance.
12. We computed *t*-tests for the 30 comparisons detailed in (11), again contrasting survivors and nonsurvivors to maintain sample independence. After the 1977 drought, males were significantly larger ($P < .01$) in all variables except wing chord, tarsus length, and principal component 2. Females were significantly larger ($P < .05$) in all variables except weight and tarsus length, with principal component 2 on the borderline ($P = .066$). The combined group was significantly larger ($P < .001$) in all variables except principal component 2.
13. The three largest standardized coefficients of the discriminant function for males alone were for bill depth (1.00), weight (.85), and bill width (.56), and the three largest $\Delta\bar{w}/\bar{w}$ values for male univariate characters were again for bill depth (.22), weight (.20), and bill width (.15). The corresponding results for the female group were different; the largest standardized discriminant function coefficients were for bill length (−1.21), bill length at a depth of 4 mm (.90), and bill depth (.55), and the largest $\Delta\bar{w}/\bar{w}$ values were for bill length at a depth of 4 mm (.40), bill depth (.25), wing cord (.22), bill length (.20), and bill width (.20).
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Heart Imaging with Cationic Complexes of Technetium

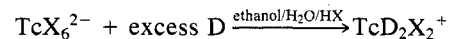
Abstract. The cationic technetium-99 complex $\text{trans-}[\text{}^{99}\text{Tc}(\text{dmpe})_2\text{Cl}_2]^+$, where *dmpe* is bis(1,2-dimethylphosphino)ethane or $(\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2$, has been prepared and characterized by single-crystal, x-ray structural analysis. The technetium-99m analog, $\text{trans-}[\text{}^{99\text{m}}\text{Tc}(\text{dmpe})_2\text{Cl}_2]^+$, has also been prepared and shown to yield excellent gamma-ray images of the heart. The purposeful design, characterization, and synthesis of this technetium-99m radiopharmaceutical represents a striking application of fundamental inorganic chemistry to a problem in applied nuclear medicine.

In the practice of diagnostic nuclear medicine, some chemical form of a photon-emitting isotope is administered to a patient with the goal of having this isotope localize in a specific organ. Subsequent scanning of the organ with a gamma-ray camera provides valuable diagnostic and prognostic information by an essentially noninvasive technique (1, 2). Technetium-99m is the isotope of choice for diagnostic nuclear medicine because of its optimal nuclear properties, its diverse chemistry, and its general availability (3). With the use of $^{99\text{m}}\text{Tc}$ in various chemical forms, it is now possible to image a variety of organs, including the brain, kidneys, lungs, liver, and bones; fully 85 percent of all diagnostic procedures in nuclear medicine are performed with $^{99\text{m}}\text{Tc}$ (4). However, it has not yet been possible to image normal heart muscle with a $^{99\text{m}}\text{Tc}$ radiopharmaceutical. It is estimated that in 1977 over 600,000 deaths in this country were attributable to myocardial infarction (heart attack) (5), and it has been noted (5) that many of these deaths could be eliminated if the high-risk patient could be identified at the earliest possible time. It has thus been a long-standing, but elusive, goal of diagnostic nuclear medicine to develop a $^{99\text{m}}\text{Tc}$ radiopharmaceutical that would accumulate in normal heart tissue and thereby allow the early evaluation of the extent of damage resulting from myocardial infarction (6).

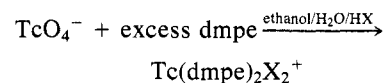
It is known that isotopes of the group I cations accumulate in normal heart tissue, ^{43}K , ^{81}Rb , and ^{129}Cs all having been used to provide gamma-ray images of the heart (7). It is also generally accepted that these cations accumulate through involvement with the Na^+ , K^+ -dependent adenosinetriphosphatase system; that is, they function as K^+ analogs. On this basis it was suggested that Tl(I) might also function as a K^+ analog and therefore accumulate in the heart (8). Thallium(I) does indeed localize in heart tissue, and ^{201}Tl is currently the agent of choice for myocardial imaging (9). However, relative to $^{99\text{m}}\text{Tc}$, ^{201}Tl is a poor radionuclide for procedures in nuclear

medicine; it is expensive, it has a photon energy that is too low for optimum imaging, and a large dose must be administered to the patient in order to obtain a reasonably high count rate (10). We postulated that +1-charged complexes of $^{99\text{m}}\text{Tc}$ might mimic the in vivo behavior of Tl(I) and be taken up by normal heart tissue (11). Prior to this work (11), no cationic complexes of $^{99\text{m}}\text{Tc}$ had been prepared and evaluated as radiopharmaceuticals as far as we know, presumably because knowledge was lacking about the synthetic and coordination chemistry of technetium. We report here on the preparation, characterization, and evaluation as a potential heart-imaging agent of a water-soluble, +1-charged complex of technetium.

Using milligram amounts of ^{99}Tc , one can prepare cationic complexes of Tc(III) by the reaction of chelating phosphine or arsine ligands (D) with the readily available hexahalogenotechnetium(IV) complexes TcX_6^{2-} ($\text{X} = \text{Cl}, \text{Br}, \text{I}$) (11, 12):



This reaction depends upon the reducing power of the excess arsine or phosphine ligand to convert Tc(IV) to Tc(III). When D is *dmpe*, or bis(1,2-dimethylphosphino)ethane, $(\text{CH}_3)_2\text{P}-\text{CH}_2\text{CH}_2-\text{P}(\text{CH}_3)_2$, the cationic product is water-soluble and is readily purified by aqueous ion-exchange chromatography. The $[\text{Tc}(\text{dmpe})_2\text{X}_2]^+$ complexes may also be prepared from pertechnetate, TcO_4^- , the chemical form in which technetium is provided by the commercial $^{99\text{m}}\text{Tc}$ generators used in hospitals (1). In this case also, the reducing power of the excess phosphine ligand converts Tc(VII) to Tc(III):



This preparation is readily conducted in greater than 90 percent yield using "no carrier added" $^{99\text{m}}\text{TcO}_4^-$ produced from commercial generators.

The $[\text{Tc}(\text{dmpe})_2\text{X}_2]^+$ complexes are readily identified in terms of their