

On the Inheritance of Handedness

II. Selection for sinistrality in mice

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L EFT-HANDEDNESS is not unique to human beings. It was previously reported that mice of highly inbred strains exhibit an enduring right- or left-handedness, and that this behavioral dimorphism was not genetically acquired¹. These findings led to a reanalysis of human data pertinent to the genetic hypothesis. Although substantial parent-offspring correlations were found to exist for human hand preference, mechanisms of transmission genetics could not be held responsible for the maintenance of human dextrality or sinistrality². Thus, while the alternative forms of human laterality are certainly heritable, the influences responsible for the transmissibility of hand preference variation must be of environmental or cultural origin. Since it was not known whether cultural transmission might be similarly responsible for paw preference variation in mice, selection for right- and left-paw preference was conducted using mice of the C57BL/6J strain. Culturally transmitted behavioral variation has been previously documented in genetically uniform mice³. The experimental results show that neither qualitative nor quantitative indices of paw preference were responsive to selection pressure. Thus, monomanual preference in laboratory reared inbred mice is neither maintained by transmissible cultural influences associated with the parental phenotypes, nor is it maintained by a residue of heritable genetic variation.

Materials and Methods

Mice of the C57BL/6J strain were obtained from the production branch of The Jackson Laboratory. This strain has been maintained by brother-sister inbreeding for beyond 90 generations. The details of the behavioral testing were similar to those previously reported¹. Briefly, mice were deprived of food for 24 hours and were placed in testing cubicles in which a feeding tube was equally accessible from the right or the left. Sweetened rolled

wheat was placed in the tube, and 50 single paw reaches were recorded for each mouse. Each subject's score was defined as the number of right paw

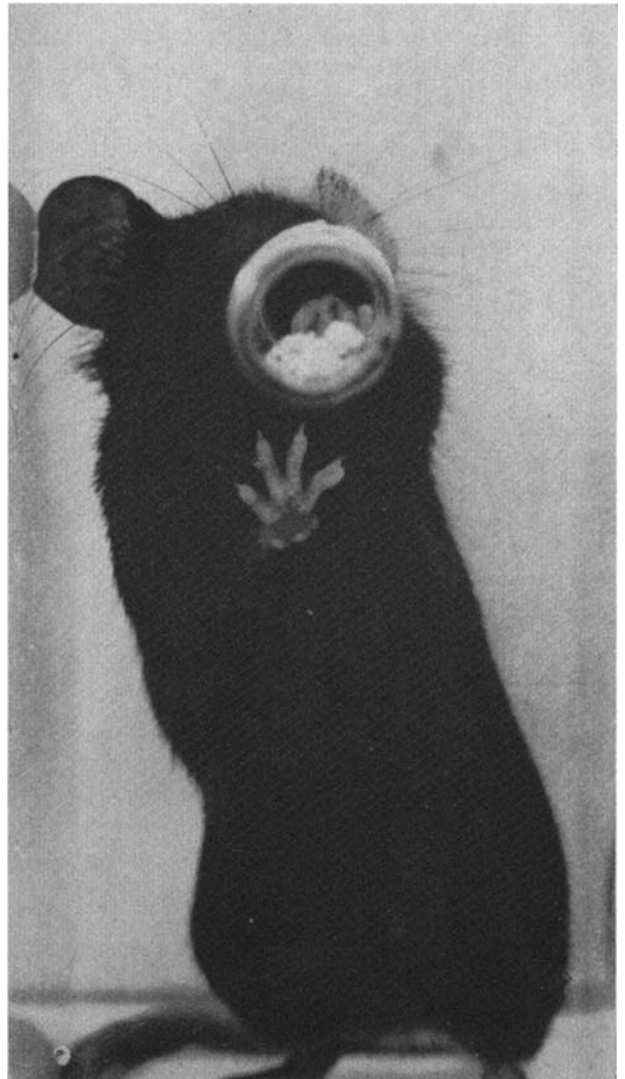


FIGURE 1—A left-handed C57BL/6J female mouse from the third generation of selection. Both of her parents and grandparents were right-paw preferent.

Dr. Collins is staff scientist, The Jackson Laboratory, Bar Harbor, Maine 04609. Supported by research grants MH 11327 and MH 1775 from the National Institutes of Health. The principles of laboratory animal care as set forth by the National Society for Medical Research are observed in this laboratory. The author wishes to thank Geddes W. Simpson, Jr., for able assistance.

entries in 50 observations (RPE's). Classifications R and L were assigned to individuals scoring more than 25 RPE's, and less than 25 RPE's, respectively. Twenty-two parental pairs were chosen from a base population G_0 on the basis of their initial and retest performance. Four types of matings were made in each generation, R-R, R-L, L-R, and L-L, where the first letter designates the phenotype of dam, and the second, the phenotype of sire. Offspring from the four parental combinations were tested for paw preference at 8 weeks of age. Selection was conducted through three successive generations.

Results

Table I summarizes the frequencies of R and L offspring for three generations of selection. Each parental class, R-R and L-L, produced approximately equal numbers of right and left paw preferred offspring of either sex ($\chi^2 = 0.03$). Whereas the concordant parental combinations each possessed zero phenotypic variance on a qualitative scale, the progeny from each combination reproduced approximately the maximum possible phenotypic variance. The discordant parental classes, R-L and L-R, yielded similar results ($\chi^2 = 0.001$). There was no differential production of phenotypes for any parental combination. The proportion of dextral mice given a dextral dam was 0.478, and the proportion of dextral mice given a sinistral dam was 0.483 ($\chi^2 = 0.009$). The proportion of dextral mice given a dextral sire was 0.491, and that given a sinistral sire was 0.472 ($\chi^2 = 0.167$). Lateral preference was not associated with the sex of offspring. The proportion of dextral female mice was 128/259 or 0.494 and the proportion of dextral male mice was 129/267 or 0.483.

Since it was conceivable that response to selection might be masked on a qualitative scale, but detectable on a quantitative index, response to selection was analyzed using the individual RPE scores.

Table I. Frequencies of dextral and sinistral offspring for three generations of selection

Gen.	Parental combination	Females		Males		Total	
		R	L	R	L	R	L
S ₁	R-R*	9	6	4	13	13	19
	R-L	9	5	4	7	13	12
	L-R	1	3	1	3	2	6
	L-L	7	3	5	4	12	7
S ₂	R-R	24	19	25	22	49	41
	R-L	15	21	17	22	32	43
	L-R	8	3	3	4	11	7
	L-L	15	20	31	18	46	38
S ₃	R-R	10	16	14	9	24	25
	R-L	1	3	1	2	2	5
	L-R	4	5	2	6	6	11
	L-L	11	19	10	17	21	36
Total	R-R	43	41	43	44	86	85
	R-L	25	29	22	31	47	60
	L-R	13	11	6	13	19	24
	L-L	33	42	46	39	79	81

* First letter designates the phenotype of dam; the second letter, the phenotype of sire.

Figure 2 illustrates the quantitative response to selection for the R-R and L-L parental combinations. There was no detectable response to selection for any generation using this index. Realized heritabilities were very near zero.

Figure 3 summarizes the paw preference scores for 858 C57BL/6J mice. These data include the results of the selection experiments as well as all data previously collected using this strain. The distribution of paw preference scores is distinctly bimodal with broad flat minima that extend 13 RPE units to either side of the 25 RPE midpoint. Forty percent of the subjects scored in the two most extreme class intervals, 0-2 and 48-50 RPE's. An additional 18 percent scored in the next most extreme intervals, 3-5 and 45-47 RPE's. Only 22/858 or 2.6 percent of all mice studied could be included in the midmost class interval 24-26 RPE's.

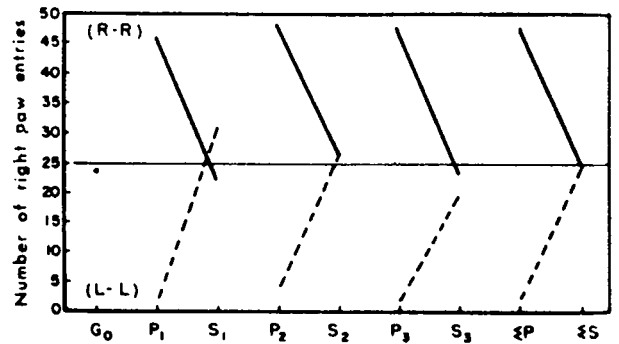
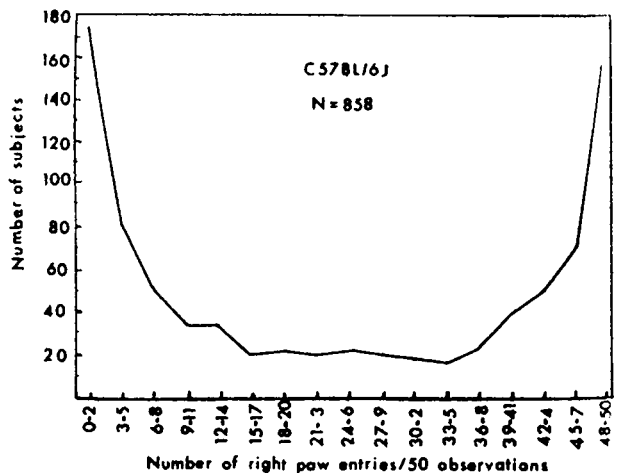


FIGURE 2.—Quantitative response to selection for paw preference in mice. The end points of each line depict the mean number of right paw entries observed for the selected parental combinations, R-R and L-L, and those for the resulting progeny. The extreme right graphs represent the response to selection summed across three generations.

FIGURE 3.—Frequency distribution of the number of right paw entries for 858 C57BL/6J mice. These data include the results of the present experiment as well as data previously collected. The abscissa is divided equally into 17 blocks of 3 RPE's.



The dichotomous nature of lateral preference in mice is emphasized by these data. Ambilaterality is surprisingly infrequent. Deleting the midmost class interval, 47.3 percent of all mice studied could be designated as being dextral, and 52.7 percent, as sinistral. The slight excess of sinistral mice, while provocative, is not statistically significant ($SE = 1.7$ percent).

Discussion

The inbred mouse has provided a striking analog, if not a homolog, to human handedness. Individuals in both species use one hand preferentially in a free-use task, the preference extends to other tasks, the behavioral asymmetry is enduring, ambilaterality is relatively infrequent, and the preferred hand is often the superior one on a force-use task.

Three generations of selection for right- and left paw preference failed to elicit changes in the qualitative or quantitative indices of dextrality or sinistrality. Accordingly, it appears highly doubtful that paw preference variation in C57BL/6J mice is maintained by a residue of heritable genetic variation, or that it is significantly influenced by cultural factors associated with the phenotypes of the parents. The lack of a detectable cultural inheritance of paw preference in mice stands in contrast to the case in man. The crystalization of pressures for uniformity of hand preference within the human family unit is well known⁸, and these influences have been found to be well suited for the maintenance of a small but stable incidence of sinistrality in the general population².

If genetic mechanisms do not specify the alternative forms of laterality, perhaps they maintain variation in asymmetry according to a more subtle process. Parsons and Howe⁴ observed the distributions of 29 bilateral skeletal variants in mice and reported frequent excesses of symmetrical types, variants present or absent on both sides, over asymmetrical types, variant present on one side. They interpreted this as representing a form of "morphogenetic homeostasis" by which symmetrical skeletal forms were favored over asymmetrical types. One may hypothesize that if genetic mechanisms do tend to insure the symmetry of homologous forms, then variation in lateral function might be engendered without specification. Biased or unbiased environmental perturbations acting upon a relatively balanced system may inevitably initiate functional one-sidedness. A central feature of a finely tuned equilibrium may be, in fact, its insta-

bility. Such a covert genetic influence would not be without benefits. Since dextral and sinistral forms would be options reserved for individual adaptation, populations would exhibit great plasticity in meeting environmental demands. Essential structural symmetry could be safeguarded against the potentially degrading effects of prolonged selection for uniformity of one functional alternative.

Two general considerations regarding laterality emerge from these studies. First, the infrequency of ambilaterality observed in mice suggests that lateral specialization may be more of a necessity than a luxury. The atypical individual is not one who exhibits a strong lateral bias, but rather is one with no marked lateral dominance. Second, the elaboration of a differentiated handedness does not appear to be a recent product of human evolution. The phylogenetic perspective afforded by the mouse suggests that variation in functional asymmetry may be a far more primitive dimorphism than has been commonly believed.

Summary

Further studies of paw preference in mice are presented. Three generations of selection for dextrality and sinistrality were conducted using C57BL/6J inbred mice. Neither qualitative nor quantitative indices of paw preference were responsive to selection pressure. Approximately one-half the progeny from the concordant parental combinations, R-R and L-L, were dextral, and one-half, sinistral. Offspring from the discordant parental pairs, R-L and L-R, yielded similar findings. These results suggest that paw preference variation in mice is neither maintained by a residue of heritable genetic variation nor by transmissible cultural influences associated with the parental phenotypes. Of 858 C57BL/6J mice tested, 52.7 percent exhibited left paw preference.

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