Behavior Genetics, Vol. 22, No. 4, 1992

Are Paw Preference Differences in HI and LO Mice the Result of Specific Genes or of Heterosis and Fluctuating Asymmetry?

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Received 18 Oct. 1990—Final 2 Dec. 1991

Collins (1985) has described two separate mouse strains, obtained by selective breeding, which differ in having high (HI) or low (LO) degrees of paw preference on a standard test. In this paper I argue that the differences between these strains may not be due to a specific gene (or genes) but, instead, probably reflect differences in the total heterozygosity of the strains, such that the HI strain is more heterotic than the LO strain. Greater degrees of heterozygosity are argued to buffer against fluctuating asymmetry and hence result in a greater degree of paw preference.

KEY WORDS: pawedness; handedness; mice; degree of lateralization; heterosis; HI and LO strains of mice; fluctuating asymmetry.

INTRODUCTION

Lateralization of function can be assessed in terms of two separate measures: the *direction* of lateralization, indicating whether the left or the right half of a system is better at or prefers to carry out a task; and the *degree* of lateralization, indicating the magnitude of the difference between the right and the left sides. Symbolizing performance of right and left sides by R and L, then a typical laterality index (LI) can be calculated

Preparation of the revised version of this paper took place while I.C.M. was in receipt of a Commonwealth Fellowship at the University of Waterloo, Ontario, Canada.

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0001-8244/92/0700-0435$06.50/0

as LI = (R−L)/(R+L), so that direction of lateralization is *sign*(LI), whereas degree of lateralization is |LI|.

Studies of human handedness (Annett, 1985; McManus, 1985; McManus and Bryden, 1991) are in general agreement that *direction* of hand preference is under genetic control, with an increased incidence of left-handedness in the offspring of left-handers. Calculation of a conventional correlation between parents and offspring produces a deceptively low value of about 0.11, since the high degree of randomness implicit in the model due to fluctuating asymmetry means that the correlation is inevitably very low. Nevertheless with an *N* across studies of about 72,600, there is no disputing the significance of the correlation (McManus and Bryden, 1991). In studies of the inheritance of *degree* of handedness in human populations, McManus (1979, 1985) found a nonsignificant correlation of 0.045 between the degree of handedness of parents and the degree of handedness of their offspring, while Bryden (1979, 1982), Porac and Coren (1981), and Bryden (1988) found significant parent–child correlations of 0.21, 0.10, and 0.19. Since these measures do not include the large randomness component implicit in assessing degree of lateralization, the implication is that in man the principal form of laterality that is under genetic control is direction of handedness rather than degree.

In a series of important papers, Collins (1968, 1975) has investigated the inheritance of paw preference in mice, using a simple, elegant procedure for measurement whereby on 50 occasions the animal has to use one paw or the other to retrieve a piece of food from a narrow cylindrical feeding tube. The number of right-paw entries (RPE) is counted, and a score of 50 indicates strong right-paw preference, a score of 0 indicates strong left-paw preference, and a score of 25 indicates absent paw preference. The measure is reliable over a 4-day interval (Collins, 1968), a 2-week period (Schmidt *et al.,* 1991), a 4-week period (Collins, 1968), and an 8-week period (Neveu *et al.*, 1988). Degree of lateralization can be measured as the number of preferred paw entries (PPEs), calculated as max(RPE,50–RPE). In the population as a whole almost exactly half show a right-paw preference (i.e., 26–50 RPEs) and half show a left-paw preference (i.e., 0–24 RPEs). Selective breeding studies by Collins (1969) showed that there was no evidence that *direction* of paw preference in the mouse was under genetic control. That conclusion is compatible with the human data on handedness, be it that of McManus (1985) or Annett (1985), since in each model there is an allele which, when homozygous (the CC or RS −/− genotypes, respectively), results in exactly 50% of left-handedness or -pawedness. There is, therefore, no transmissible control of hand preference in a strict sense, direction of

lateralization in individual organisms being determined entirely by fluctuating asymmetry. The mouse, therefore, would seem to have only one of the two alleles which appear to control direction of laterality in humans.

An important difference arises between the mouse and the human studies, however, with regard to the inheritance of degree of lateralization. Collins (1985) has described an extensive selective breeding study of degree of pawedness resulting in the eventual isolation of strains with high (HI) and low (LO) degrees of pawedness (mean PPEs of about 43.5 and 36.5, respectively). This result is difficult to reconcile with the human data, since it might be expected in evolutionary terms that if mice have a gene or a set of genes that determine degree of pawedness, then similar genes might also have developed in humans. In this paper I wish to consider the way in which Collins' HI and LO mice have been selected and to question whether in fact they truly represent evidence for direct genetic control over lateralization. Instead I suggest that these strains may differ principally in their degree of heterozygosity and that this results in differences in the amount of fluctuating asymmetry. Hence there is a lack of buffering to "biological noise," which then causes different degrees of lateralization.

COLLINS' SELECTIVE BREEDING PROGRAM

Collins (1985) described the selective breeding program for the HI and LO strains in some detail. The program began with eight strains of mice, six of which (BALB/cJ, C57BL/6J, DBA/2J, LP/J, RF/J, and SM/J) were fully inbred, but showed remote common ancestry, and were known to be widely different at polymorphic loci; they may each be assumed to be homozygous at most of their loci. The remaining two partially inbred strains, of *Mus castaneus* and *Mus molossinus*, have been categorized as possibly separate species of *Mus* and differ in many of their loci from the conventional laboratory strains. The purpose of using these very different strains was to introduce a wide range of genetic variation into the foundation population (generation zero; G0). G0 was produced by systematic intercrossing between the eight initial inbred strains, and it can be assumed that the foundation population, of some 327 mice, contained principally heterozygous individuals obtained from crosses between different inbred strains.

From the foundation population, the HI line was started by selecting only mice with PPE scores of 48–50, and the LO line was started by using only mice with PPE scores of 25–40. As breeding continued, the ceiling for retention of animals for the LO line was reduced from its

initial value of 40. Selection continued for 10 generations. Analysis of the phenotypes of each generation (Collins, 1985, Fig. 7) shows that, from generation 3 onward, there was a continuing phenotypic divergence of the HI and LO strains.

Despite the clear selection that was eventually obtained, the interpretation of these results is not clear. As Collins (1990) points out, the data "generates some puzzles. For example, the heritability estimate from the foundation population was negative, and the first generation realized heritability for the HI line was indeed negative."

IS THERE A SINGLE LOCUS CONTROLLING DEGREE OF LATERALIZATION?

Consider that there is some locus with two alleles, *h* and *l*, which cause a high and low degree of lateralization, respectively. Selective breeding has resulted in the HI strain having a higher proportion of the *h* allele than does the LO strain. If this is the case, then the *h* and *l* alleles must have come from somewhere, and that place is, of course, from the initial eight inbred strains which were used to create the foundation population. However, those foundation strains were necessarily homozygous at most loci, and therefore each must either have contained *hh* or *ll* genotypes, which should have manifested as high and low lateralized phenotypes, respectively. Assessment of the phenotypes of the original eight strains should then have found some with a degree of lateralization at least as high or as low as those in the HI and LO strains (which are still undergoing selection), and probably higher since (unlike the selected strains) they are purely homozygous. Unfortunately the extent of lateralization does not appear to have been studied in the eight original inbred strains (Collins, 1986, personal communication). A similar argument applies if degree of lateralization is determined by many alleles at a single locus: the eight original strains must differ in degree of lateralization, with at least one being as strongly lateralized as the HI strain and one as weakly lateralized as the LO strain. [To anticipate a subsequent part of this paper, it should also be noted that even if degree of lateralization were secondary to fluctuating asymmetry which was under direct genetic control (for a review of this possibility see Livshits and Kobyliansky, 1989), then the eight original strains should, by the same argument, have differed in their degree of lateralization]. Only if degree of lateralization is truly polygenic, being determined by many alleles at many loci, may the original populations show less extremes of lateralization than do the HI and LO strains. In that case, although each strain will be homozygous, they will be homozygous for different loci,

and the effects of those loci will, on average, tend to cancel one another out, so that the HI and LO strains may then be more extreme than the original strains. Detailed scrutiny of the selective breeding results suggests that the data are probably not compatible with the smooth, even selection that might be expected of a polygenic system with many alleles at many loci. Within the HI strain there is indeed a fairly smooth increase in mean PPE (Collins, 1985, Fig. 7). However, within the LO strain, the selection is more erratic. This is particularly the case between generation 7 and generation 8, when the mean PPE score suddenly jumps to a value about 4 standard errors higher than that in the previous generation and then falls by 2.5 standard errors in the next generation. These results are surprising and suggest that other factors may be influencing selection. Although, because of relatively small samples of parents in each generation, it is possible that these differences may reflect genetic drift, this seems unlikely in view of the size of the standard errors reported at each generation.

THE ROLE OF HETEROZYGOSITY IN DETERMINING FLUCTUATING ASYMMETRY

The biological literature contains a number of studies that have investigated the role of heterozygosity in determining the extent of asymmetry. The overall extent of heterozygosity has been known for many years to be a determinant of overall reproductive success and to determine both morphological variability (Lerner, 1991; Thoday, 1956; Waddington, 1957; Bulman-Fleming *et al.*, 1991a) and behavioral variability (Hyde, 1973; Wainwright, 1981; Maggio and Whitney, 1986; Warren, 1988; Kronenberger and Medioni, 1985; Lassalle *et al.*, 1991). A loss of heterozygosity due to intensive selection is known by animal breeders to depress growth, viability, and fertility, although its effects can sometimes be mitigated against by simultaneous balancing selection for overdominance (Vrijenhoek *et al.*, 1990).

Fluctuating asymmetry refers to deviations from bilateral symmetry which are not heritable or selectable in genetic experiments (Palmer and Strobeck, 1986). As such they represent ontogenetic anomalies which can be seen as indicating that an organism's development is subject to random fluctuation, representing " 'developmental noise' or minor environmentally induced departures from some ideal developmental program" (Palmer and Strobeck, 1986). As an example of such noise, Bulman-Fleming and Wahlsten (1991) concluded that within-litter differences in the incidence of callosal agenesis are the result of "non-genetic variability resulting from stochastic events early in development and intrinsic

to the fetus." Typically, fluctuating asymmetry is measured directly by assessing the length or overall size of bilaterally symmetric organs such as the long bones or teeth. In general, it has been found that within species, the more heterozygous an individual or a population, the lower the extent of fluctuating asymmetry, and the greater the extent of inbreeding, the greater the extent of fluctuating asymmetry (Palmer and Strobeck, 1986). In humans it has been shown that dental fluctuating asymmetry correlates well with the extent of adverse genetic and environmental conditions (Bailit *et al.*, 1970). The potential for environmental influences upon fluctuating asymmetry in the long bones is shown in detailed week-by-week studies of tibial growth in children, which demonstrate that a substantial amount of variance in rate of growth of one leg is not correlated with rate of growth in the other leg (Hermanussen *et al.*, 1989). The accumulation of such differences due to environmental factors would result in variance between individuals.

Homozygosity due to inbreeding has been associated with increased morphological variability, resulting in increased fluctuating asymmetry (Soulé, 1979), and has been conceptually ascribed to a lack of "buffering" or "developmental stability" and more directly related by Soulé (1982) to randomness in the form of Brownian motion or other molecular events. Recent examples of the role of inbreeding in determining fluctuating asymmetry are those of Wayne *et al.* (1986) on the asymmetry of the skull in the African cheetah, which has shown an "evolutionary bottleneck in the past" (O'Brien *et al.*, 1986), and of Leary *et al.* (1985) of the increased variation in morphological asymmetry in relation to overall homozygosity in the rainbow trout, asymmetry also being related to rate of development (Danzmann *et al.*, 1986).

A MODEL OF THE HI AND LO STRAINS OF MICE

I propose that the degree (as opposed to direction) of lateralization in mice is determined by the overall level of heterozygosity. The presence of homozygosity results in a lack of developmental buffering and an increase in biological noise, which, in turn, results in an increased degree of fluctuating asymmetry. In situations in which directional asymmetry is normally present (e.g., human handedness), this results in a return from the normal inequality of R and L forms toward the more primitive situation of a 50:50 mixture of directions of lateralization, as has been proposed for handedness in human mental subnormality (Batheja and McManus, 1985). Additionally, whether or not directional asymmetry is present, biological noise results in a disruption of the normal control of processes such as pawedness so that, instead of one paw becoming pre-

ferred, there is a lack of preference. I therefore propose that the HI mice are more heterozygous than the LO mice and that selection has been for high or low degrees of heterozygosity in general, rather than for genes that directly control degree of lateralization.

The hypothesis is compatible with several otherwise difficult observations concerning the HI and LO mice.

(i) The LO mice have less reproductive success than do the HI mice, with a greater frequency of nonreproductive mating pairs and, on average, one offspring fewer in each litter (Collins, 1985). This is similar to other findings of smaller litter sizes and lighter pups in inbred rather than hybrid strains (Wainwright, 1981).

(ii) The LO mice have a higher proportion of females than do the males. Females are necessarily more heterozygous than are males (due to having two X chromosomes rather than one) and, hence, may be better buffered from developmental noise. Therefore, female fetuses are less likely to miscarry spontaneously *in utero* than are male fetuses. [It should also be noted that female mice in general are more strongly lateralized than are male mice (Collins, 1985; Signore *et al.*, 1991), as would also be predicted from their increased heterozygosity; the study of mice with testicular feminization (Nosten *et al.*, 1989) strongly suggests that testosterone is a key component of the difference between male and female mice.]

(iii) Mice of the HI strain have a more accelerated neonatal development than do those of the LO strain (Mikuni-Durkee, 1982), as do heterozygotes in general (Singh and Zouros, 1978).

(iv) LO mice are more likely than HI mice to show autoantibodies to DNA (Bailey *et al.*, 1985). Selective breeding programs have resulted in a range of animal models of the common autoimmune disorders, many of which are recessive conditions. The implication is that LO mice manifest similar problems because they are more likely to be homozygous and, as a result, to manifest recessive disorders.

(v) LO mice are more likely to be homozygous than are HI mice. Collins *et al.* (1985) describe the haplotypes of HI and LO mice for the H-2 histocompatibility complex. Given the proportions of each haplotype, one may use the Hardy–Weinberg equilibrium to calculate the proportion of heterozygotes in the population: 67.7% of HI mice are heterozygotes, compared with only 61.3% of LO mice, a difference that is in the expected direction. Whether it is statistically significant is difficult to ascertain. Collins *et al.* (1985) have also assessed the genotypes at a number of other loci, although insufficient data are reported to assess whether there are differences between HI and LO mice.

(vi) The HI and LO strains have both lost more haplotypes from

their gene pool than would have been predicted due merely to genetic drift and loss of neutral alleles. This is reflected in the far higher rate of heterozygosity for the H-2 locus in the G0 population than in either of the selected strains (80.3%). This finding may be the result of selection both for heterozygosity and for homozygosity. In the case of selection for homozygosity (in the LO mice) there would be a loss of heterozygotes, resulting in the loss of the particular haplotype associated with that heterozygous pair. Loss would be faster than that due to chance and random drift. For the case of selection for heterozygosity (in the HI mice), the system may also be vulnerable to loss, since 50% of the offspring of matings between heterozygotes (AB × AB) are homozygous at a particular locus (i.e., AA or BB) but may still be retained in the next generation due to *other* loci still being heterozygous and thus being selected for. The result would be a loss of haplotypes at an individual locus, despite an increased heterozygosity overall.

(vii) Selection for HI and LO strains should be asymmetric, since it is easier to select for homozygosity than for heterozygosity. Other studies selecting for increased or reduced fluctuating asymmetry have found that selection is asymmetric (Maynard Smith and Sondhi, 1960; Reeve, 1960). Homozygous offspring breed true and therefore will produce more offspring like themselves. That, however, is not the case for heterozygous offspring, only 50% of the offspring of which will also be heterozygotes, the other 50% being homozygotes of the two alleles involved. Collins (1985) claims that the rate of selection is the same for both HI and LO strains (his Fig. 7), but inspection of Fig. 7B of Collins (1985) shows, on the more appropriate logit scale, that from generation 0 the total selection is nearly twice as great for the LO strain (0.55 unit) as for the HI strain (0.28) unit). That the selection for each strain is not linear is shown in Collins' Fig. 7B by the poor fit of the regression lines, 13 of the 22 points being more than one standard error from the line. The lack of symmetry in the selection is also shown in Fig. 8 of Collins (1985), which gives distributions of RPE scores for the HI and LO strains. Ignoring the 29.5% of HI mice and 27.1% of LO mice which are neither high scorers (48–50 PPEs) nor low scorers (25–40 PPEs), then 8.55 times as many LO mice are in the low target group as are in the high group (89.5 vs. 10.5%), compared with only 1.65 times as many HI mice in the high target group as in the low group (62.2 vs. 37.8%). This result cannot be rationalized away as due to the histogram bin widths being different (48–50 paw entries vs. 25–40 paw entries) and, hence, the selection targets being of different difficulties, since if one looks at the foundation population (Collins, 1985, Fig. 6), then almost precisely equal numbers of animals are in the high and the low groups (104 and 112;

31.8 and 34.2%, respectively), so that selection should have been equally easy for each group.

(viii) If selection is for homozygosity, then it should show more erratic behavior than would be expected if one were selecting for a conventional polygenic or multiallelic system. Consider the problem of generation N at which one mouse has been selected which has genotype AA, and another mouse genotype BB at a particular locus. Both are homozygous and selection is appropriate. If, however, these mice mate to produce the next generation, their offspring are necessarily of genotype AB and are heterozygous. With small populations there might, therefore, be sudden large reversals of selection. One such reversal has already been described in the LO strain, between generation 7 and generation 8.

HETEROZYGOSITY, FLUCTUATING ASYMMETRY, AND DEGREE OF PAW PREFERENCE

In this paper I have proposed that LO animals are relatively more homozygous, therefore showing more fluctuating asymmetry, which results in their showing a lesser degree of paw preference. The latter part of the argument might, at first, seem somewhat paradoxical. If greater fluctuating asymmetry means an increased variance in lateralization, then surely it would be expected that LO mice would be *more* lateralized, not less. That is to confuse the nature of two types of asymmetry, however. These are fluctuating asymmetry, which, even within an individual, represents a random, chance fluctuation in the ontogeny of a number of morphological and behavioral processes, and paw preference, which for an individual animal is highly directional. It is only at the population level that animals shows random direction of paw preference. In contrast, they show fluctuating asymmetry in individuals, as well as in the population.

Paw preference represents a well-organized, coherent behavioral response to a complex environmental challenge, that of carrying out a difficult and novel unimanual task which is not part of the animal's typical, ecologically based, repertoire of behaviors. Like all well-organized behaviors it involves the seamless integration of a range of discrete and separate behavioral components, including visual orientation, postural positioning, tactile perception, and fine motor coordination. An organism which is strongly lateralized is more likely to have integrated these components successfully and be able to carry out the task efficiently. (An empirical prediction of such a theory is that strongly lateralized animals will be faster and more efficient at the task.) An organism that carries out a task well will be less liable to disruption by external

influences. To use a genetic metaphor, derived from the developmental genetic concept of canalization (Waddington; 1957, 1960; Waddington and Robertson, 1966; Thompson and Rook, 1988), the strongly lateralized animal can be seen as "behaviorally canalized." This concept can be seen in the comparison of maternal behavior in inbred and hybrid strains. "The hybrid animals were more active in manipulating their environment. . . . It is . . . in the organisation of their responses that they differed [from inbreds]. . . . [which] were unable to integrate their responses into an effective behavioral plan . . . . [T]he measures that discriminated between the groups were . . . those that reflected the temporal organisation of the behavior" (Wainwright, 1981, p. 705). Genetic canalization reflects the ability of an organism to stabilize its phenotypic environment so that a gene will manifest similar phenotypic results against a range of genotypic backgrounds (Maynard Smith *et al.*, 1985). Similarly, a behaviorally canalized organism will produce equivalent and appropriate behaviors despite wide variation in genotypic and environmental backgrounds. It is of importance to note that the initial lack of genetic canalization in the presence of a new mutation is reflected in increased fluctuating asymmetry, which subsequently declines after further selection (Clarke and McKenzie, 1987).

The neural organization of paw preference is very unclear. It can be assumed, nevertheless, that it involves a number of discrete neural subsystems, some of which will be bilaterally organized and, as a result of fluctuating asymmetry, likely to be of different "strength" or functional efficiency on the two sides. Increased fluctuating asymmetry will make such differences larger and make it more likely that the better side for one component is more likely to be on the opposite side to that which is better for another component. In effect, the developmental noise of fluctuating asymmetry randomly shuffles or rearranges what would otherwise have been an ordered system. The well-canalized, well-buffered organism, in contrast, either will have small differences between sides or will have its better components tending to be on the same side. The present hypothesis therefore predicts that poorly lateralized animals will be those with greater fluctuating asymmetry and will be those that are more homozygous; the more strongly lateralized animals show less variance between individuals and, hence, are better canalized (Maynard Smith *et al.*, 1985).

Evidence from lesion studies suggests that there are cortical components to preference in both the rat (Kirk, 1935; Webster, 1977; Webster and Shoup, 1975) and the cat (Burgess and Villablanca, 1986), with preference reversing after cortical damage, particularly if it involved the anterior or primary sensorimotor cortices. Components of the extrapy-

ramidal motor system also seem to affect preference, studies having found that 6-hydroxydopamine lesions of the lateral hypothalamus (Uguru-Okorie and Arbuthnott, 1981) and the substantia nigra and caudate nucleus (Siegfried and Bures, 1980) will reverse preference if injected contralateral to the preferred paw but have no effect if injected ipsilateral to the preferred paw. These results support the suggestion that innate paw preference may reflect underlying asymmetry in the nigrostriatal system (Glick *et al.*, 1977).

The role of the corpus callosum in paw preference is not clear. As it provides the principal connection between homologous cortical areas of the two hemispheres, it might be expected to be important in preference for one side or another. Empirically, however, the situation is confused. In the I/LnJ strain of mice, which shows a complete absence of the corpus callosum, it has been reported that the animals are significantly less lateralized than controls (Lipp and Waanders, 1990). The 129/J strain of mice shows a significant correlation between corpus callosum area and degree of paw preference (Ward *et al.*, 1987), while in the same study the BALB/cCF strain showed no evidence for such a relationship. In the C.B6$-+^c/+^c$ substrain of BALB/c congenic mice, in which a high proportion has abnormal callosa, there was no difference in degree of paw preference between those animals with and those without a callosum (Bulman-Fleming and Wainwright, 1991), and a similar result has been reported for BALB/cCF mice (Schmidt *et al.*, 1991; Bulman-Fleming *et al.*, 1991b). Lesioning of the corpus callosum in the rat has no effect, whether or not it is carried out in conjunction with forced practice of the nonpreferred paw, and has no influence upon paw preference (Martin and Webster, 1974). At present, therefore, it seems to be an open question as to whether the corpus callosum is important in degree of paw preference in mice or whether it is a marker for some other variable of greater importance.

PREDICTIONS OF THE MODEL

The hypothesis that HI and LO strains are distinguished principally by their degree of heterozygosity which, in turn, determines the extent of their fluctuating asymmetry, makes several clear predictions about the HI and LO strains and about degree of lateralization in mice in general.

(i) HI-strain individuals should show less fluctuating asymmetry than do LO-strain individuals, as assessed in the conventional way through the size of skeletal components such as skull bones, teeth, etc. (Siegel and Doyle, 1975).

(ii) HI-strain animals should show more heterozygosity than LO-

strain animals on a range of polymorphic markers, such as isoenzymes. In assessing this hypothesis it should be borne in mind that heterozygosity at some subset of markers is not necessarily a good predictor of heterozygosity at other subsets and that the level of fluctuating asymmetry in an organism may reflect the heterozygosity of a specific block of contiguous loci (Palmer and Strobeck, 1986).

(iii) In general, inbred animals should show a lesser degree of lateralization than do outbred animals. There is some suggestion of this in the data of Collins (1968), in which the mean number of PPEs in inbred C57BL/6J and DBA/2J mice was 39.09, compared with a mean of 39.86 in the F_1 hybrid matings between the two inbred strains. However, the difference is probably not statistically significant. It should be noted that although the difference is small (0.75 paw entries), Collins (1985) obtained a difference of only 7.0 paw entries after 10 generations of selection, averaging a selection rate of 0.7 paw entries per generation.

DISCUSSION AND CONCLUSIONS

This paper has argued that the HI and LO strains of mice may be the result not of specific genes that determine degree of lateralization but, instead, of a developmental consequence of the total degree of heterozygosity shown by the organism, with high levels of heterozygosity causing a low degree of biological noise, good canalization, low fluctuating asymmetry, a consistent pattern of lateral organization, and, thereby, a greater degree of paw preference.

The hypothesis explains several features of the HI and LO strains, as described above. However, like many hypotheses, it cannot explain everything that is known about these strains, although I would argue that in that respect it is no different from the implicit, conventional hypothesis of a simple, single genetic difference between the strains. The following list of other differences between HI and LO mice is no doubt incomplete. Lipp *et al.* (1984) found that the absolute degree of size asymmetry of the right and left cerebral hemispheres of HI mice was greater than that of LO mice, a result opposite to that predicted by the current hypothesis; it is not clear whether the direction of the asymmetry relates to the direction of the paw preference. Ward and Collins (1985) found that the absolute difference in hemispheric weights was greater in HI mice than in LO mice, a result also in the opposite direction to that expected; in that study it was reported that the direction of asymmetry did not relate to the direction of paw preference. It is also of interest that the heterozygous HET strain of mice (equivalent to the foundation population) is more similar to the HI mice than to the LO mice, as might be expected.

HI mice have also been reported to have larger brains overall than LO mice, as well as larger anterior commissures and corpora callosa (Cassells *et al.*, 1990). Such neuroanatomical differences between HI and LO animals may reflect the effect of heterosis upon myelination (Miskimins and Yu, 1988), although in other contexts it must be noted that heterosis does not always produce effects upon neural development (Wahlsten *et al.*, 1991). Ward *et al.* (1986) reported that HI mice climbed more, gnawed more often, were less often immobile and showed longer episodes of nonexploratory behavior, and Scott *et al.* (1986) reported that HI mice are more aggressive than LO mice. No obvious explanation for the latter results is apparent, although they may conceivably be construed as adaptive responses due to greater heterosis and, hence, greater behavioral canalization. That HI mice have longer tails than LO mice (Cassells *et al.*, 1990) may also be a consequence of heterosis, it being assumed that tails in mice normally have an adaptive function.

The HI and LO strains of mice are important because they may serve as an animal model for one aspect of the most important laterality for psychologists, that of human handedness and speech lateralization. It is therefore important to understand the genetic basis for what are clear differences between the two strains. The present hypothesis provides a testable explanation of several puzzling features of he HI and LO strains. It also makes several interesting predictions about differences in degree of handedness within humans. If fluctuating asymmetry due to homozygosity is the cause of reduced degree of handedness, then the model predicts the following:

(i) Right-handers with a low degree of lateralization should show evidence of increased fluctuating asymmetry, as assessed by conventional measures such as incisor width and thickness.

(ii) Right-handers with a low degree of lateralization should show increased homozygosity when assessed across a broad range of polymorphic loci.

(iii) Individuals with a greater degree of inbreeding (as in the product of cousin marriages) should show lesser degrees of lateralization than individuals who are outbred. Although this is a difficult hypothesis to test in typical Western populations, due to the relative scarcity of cousin marriages, it would be practical to assess it either in countries such as India, in which cousin marriage is a cultural norm, or in inbred communities such as the Amish and the Mennonites of America and Canada.

ACKNOWLEDGMENTS

I am grateful to Drs. M. P. Bryden, B. Bulman-Fleming, and P. E. Wainwright for their helpful discussions and criticisms of this paper.

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Edited by P. Driscoll