The inheritance of asymmetries in man and flatfish

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Policansky (1982b) has recently described the results of experiments in flat fish assymmetry which, he suggests, are evidence against the proposal of Morgan & Corballis (1978) that there is an "asymmetrical inheritance of asymmetry." In accepting his criticisms, Morgan and Corballis (1982) ask why it is that clear-

cut cases of the symmetrical inheritance of asymmetry are so rare, and what type of mechanism could account for genes that apparently encode dextrality and sinistrality. In this commentary I would like to describe a genetic model of asymmetry which clarifies possible mechanisms, which is compatible with much of Morgan and Corballis's position (in that an extra-Mendelian factor is necessary), and which can account for the inheritance of flatfish asymmetry as described by Policansky. The model has been described in detail elsewhere (McManus & Mascie-Taylor 1979), and only a brief review is given here.

The model starts from the important principle, recognised by Kant, that a unidimensional communication system, such as speech or the genetic code, is unable to disambiguate enantiomorphs (mirror images) except by comparison with other three-dimentional enantiomorphs of known properties. We therefore proposed that there must exist an intracellular "signpost," S, which points to a particular form of asymmetry. In order for an allele, A, consistently to produce an asymmetric phenotype, P, it must be able to read the signpost, even though it itself may be left–right agnosic. A second allele, B, at the same locus as A, may produce phenotype ~P, which is the mirror image of P, simply by reversing its reading of the signpost, S (i.e. by going in the direction opposite to that pointed to). Hence A and B are symmetric in their effects (although not necessarily symmetric in their case of mutation or evolution). A third allele, C, may be unable to read the signpost at all, and hence chance factors alone will determine whether individuals will be P or ~P, and overall the population of offspring will be of a racemic mixture. We may now consider a second pair of alleles V and W at a locus separate from that of A and B; V and W produce the enantiomorphic phenotypes Q and ~Q, in each case using the signpost, S, to determine the chirality of the phenotypes. Individuals of genotype AAVV will be of phenotype PQ, and those of genotype BBWW will be phenotype ~P~Q. If the signpost, S, should itself become reversed, to ~S, then genotypes AAVV and BBWW will now produce phenotypes ~P~Q and PQ respectively; in other words, the entire set of asymmetries of the organism will have been reversed. By considering independent or primary asymmetries it is therefore possible to distinguish allelic (or true "genetic" effects) from lesions of the signpost system. Elsewhere we have suggested that the very rare occurrence of a single flatfish of the species *Tanakius kitaharae* which showed atypical eye migration, atypical optic chiasm, and atypical visceral asymmetry (Hubbs & Hubbs 1945) is most parsimoniously explained in terms of signpost reversal rather than multiple genetic mutations (McManus & Mascie-Taylor 1979).

At an allelic level I would propose that "chance" alleles, C, are the baseline from which other alleles have evolved (i.e. the allele does not use the signpost information at all); this would be supported by the almost universal occurrence of fluctuating asymmetry in bilateral systems, and by cladograms such as that shown by Policansky. Alleles of type A and B would either have to mutate independently or else mutate one from the other; in either case, the more common situation would be to find just two alleles (i.e. A and C or B and C), and only relatively rarely would one find all three alleles (A, B, and C), or just the two directional alleles (A and B). Of course selection pressure could result in the loss of alleles after mutation, although it must be pointed out that there is as yet no convincing evidence of a selective advantage for any particular enantiomorphic system. The effect of developmental "noise," from whatever cause, may also be to override the directional asymmetries of A and B alleles, and to produce a phenocopy CC individual with apparent fluctuating asymmetry for some or all loci.

In the case of human handedness and cerebral dominance I have suggested that two alleles (D for dextral and C for chance) at a single locus and with additivity for the heterozygote can account for the family data in the literature (McManus 1984). Data on the inheritance of visceral *situs* also suggest a similar two-allele genetic mechanism (S for sinistral heart, C for chance). In the case of the independent asymmetries of hand clasping and arm folding (which are also independent of handedness), a triallelic system (D for dextral, S for sinistral, and C for chance) with additivity for all heterozygotes can account for the published data (McManus & Mascie-Taylor 1979). On the basis of the very limited data on flatfish asymmetry we also proposed that a triallelic system with additivity could account for the data. In the rest of this commentary I wish to suggest that Policansky's data can be accommodated by this model without the need for postulating "environmental influences." The particular genotypes of Policansky's fish will also be suggested.

Table 1 (McManus). *Summaries of the three-allele model of the inheritance of asymmetry (McManus & Mascie-Taylor 1979)*

Genotype	Phenotype	
	%Left	%Right
DD	0	100
CC	50	50
SS	100	0
DC	25	75
CS	75	25
DS	50	50

Table 1 summarises the genetic model. To fit the model to Policansky's Table 2, I have calculated, for each mating pair, the relative log-likelihoods that that mating pair could be any of the 36 possible genotype × genotype combinations, given the parental phenotypes and offspring phenotypes. A priori, the gene frequencies of S, D, and C were set equal, and to avoid values of infinity in the calculations, offspring probabilities of 0 or 1 were reset to 0.000001 and 0.999999 respectively. For each genotype combination the chi-square goodness of fit test was also calculated for the observed offspring proportions to the predicted proportions. A table was then constructed containing for each actual mating pair those genotype combinations for which the chi-square value was less than 3.84 and the relative log-likelihood with respect to the best-supported model was less than 5. From such a table one may, by heuristic methods, arrive at possible parental genotype solutions. Since the problem is a variant of the "travelling salesman" problem (Flood 1956; Sedgewick 1983) it is not possible to say with certainty that this is the only or the best solution, although two independent workers have arrived at essentially similar conclusions from the same table. Table 2 shows the hypothesised genotypes, the observed and predicted proportions of left offspring, and the chi-square goodness of fit test. Of the 20 observed matings, only 2 produce observed values which are significantly different from the predicted value at the 5% level. The total chi-square value of 31.567, with 20 df, is not significantly different from chance variation at the 5% level, suggesting that the two "significant" results are due to type I errors. The genetic model is therefore probably compatible with the data.

Table 2 shows several interesting features. If the model is correct, then it predicts that the matings 59L × 97L, 61L × 97L, and 96L × 97L should all produce only left offspring. No matings between this set of parent fish should produce only right offspring. The four Japanese fish have genotypes SS, SS, SC, and SC, suggesting a high incidence of the S allele, as would be expected. However, some Japanese individuals do seem to have the C allele, the origin of which is not clear, given the very high incidence of left individuals in the natural population. Further matings of 60L with 96L and 97L with 59L and 61L would help to elucidate this problem.

Table 2 (McManus). *Observed and expected proportion of left offspring*

		Females			
	Fish:	60L(J)	82L	91R	97L
	Genotype:	SC	DC	DD	SS
	Males				
h	*Genotype*				
		.868	.720	.484	—
(J)	SS	.875	.625	.5	1.
		.038	6.782	.500	—
		—	—	.482	—
(J)	SS[a]	.875	.625	.5	1.
		—	—	.071	—
		.831	—	—	.869
(J)	SC	.75	.5	.375	.875
		2.219	—	—	1.508
		—	.571	.239	—
	DS/CC[b]	.625	.375	.25	.7
		—	1.105	.143	—
		—	.388	.323	.753
	DS/CC[b]	.625	.375	.25	.75
		—	.014	3.4973	.011
		—	.571	.368	—
	SC	.75	.5	.375	.875
		—	1.290	.073	—
		—	.418	.175	—
	DS/CC[b]	.625	.375	.25	.75
		—	2.157	2.594	—
		—	—	.508	—
	SS	.875	.625	.5	1.
		—	—	.032	—
		.785	.510	.415	.833
	SC	.75	.5	.375	.875
		4.771	.0769	1.260	3.422

e: Chi-squared goodness-of-fit statistic given the genotypes wn along the edges.
is fish is only slightly less likely to be of genotype SC.
S and CC are usually indistinguishable without an F1 eration.
rce: Policansky 1982b.

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stcommentary

ntator D. Policansky was given the opportunity to reply to uing Commentary on his contribution in BBS 5(2), 1982.

enes know left from right?

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Boklage and **McManus** have reanalyzed the data in my commentary (Policansky 1982b). Boklage has attempted to understand the genetic system by far more detailed analyses of the data than I provided, while McManus has tried to fit the data to a model that postulates a cytoplasmic signpost. Since their approaches are quite different I consider their commentaries separately.

How could I say anything negative about **Boklage**'s commentary? His analyses show that mine were perhaps a little too simplistic, although my major conclusions are supported. I had overlooked the fact that the U.S. females do appear to have a somewhat stronger influence on the laterality of their progeny than the males do; if this is not a statistical accident then there is some type of maternal effect. Boklage's analyses do, however, support my conclusion that the laterality of the progeny is not purely due to maternal influence, as Walters (1961) had suggested, and as might have been expected by analogy with snails (Policansky 1982a; Sturtevant 1923).

Boklage's point that the left- and right-determining factors need not be allelic is interesting, although it does not affect the impression that, at least in starry flounders, the genes appear to know left from right. I agree that even Boklage's thorough analyses do not allow one to choose between a number of genetic models. One needs an enormous amount of data to distinguish even between two- and three-locus models.

McManus suggests that his signpost model provides a mechanism for the inheritance of asymmetry that is compatible with Morgan and Corballis's position (1978). This treatment raises troubling questions, as did the earlier paper (McManus & Mascie-Taylor 1979). McManus's point, as I understand it, is that there exists some type of cytoplasmic signpost which is read by an asymmetry locus "even though it itself may be left–right agnosic."

The crux of the problem, as *McManus* points out, is that there seems to be no asymmetry in space that could provide a framework for distinguishing left from right. In other words, left and right are relative terms; they have no meaning without a frame of reference. Incidentally, this is the same problem, at a larger scale, that makes it hard to see how there can be any selective advantage to a sinistral over a dextral flounder, or vice versa: It is difficult to imagine an environmental asymmetry whose effects could not be reversed simply by the fish's turning around.

The problem with the signpost analogy is that it does not seem to be heuristic. I don't think that anyone has suggested that left and right alleles can work without a frame of reference. There has to be an asymmetry in their environment for them to work on. **McManus**'s signpost seems to have the role of translator; it translates the environmental asymmetry into something that the left and right alleles can read. What is the signpost? If it is a cytoplasmic asymmetry, and it can itself become genetically reversed as McManus suggests, how does *that* locus work? In other words, hasn't McManus merely added a layer of complexity, but not done away with the need for a locus that does "know right from left"? How is understanding enhanced if we say "alleles L and R do not know left from right, but can read the signpost, while allele O cannot," instead of saying "alleles L and R are left and right determining, respectively, while allele O is nondetermining"? What experiment could test the signpost analogy against an alternative?

I certainly have no good reason for rejecting a two-locus model of this type for the inheritance of left–right asymmetry, except for parsimony. Note that **McManus**'s model is different from one specifying two asymmetry loci, each influencing the proportion of lefts and rights in the progeny, and could be coupled with such a model. But as I said above, I'm not sure how this model helps.

I should mention that the F_2 crosses alluded to in my 1982b paper will not be forthcoming. It was impossible to mark and maintain progenies of the various F_1 crosses with the time and space available. Also, as mentioned and corrected in **Boklage**'s Table 1, there was an error in my Table 2.

Author's Response

Human laterality: Matters of pedigree

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Harris has performed a valuable service in documenting historical forerunners to the idea of a maturational left–right gradient. Even the present-day interest in anatomical asymmetries of the brain, often attributed to Geschwind and Levitsky (1968), dates back to the 19th century. Then as now, however, the link between anatomical and functional asymmetries seems a tenuous one, and crude observations of the relative weights or sizes of the two sides of the brain, recorded at a single stage of development, seem unlikely to resolve theoretical questions about the role of growth gradients.

Our primary theoretical concern, unlike that of earlier writers, was to explain the apparent contradiction between early cerebral lateralization and infantile equipotentiality: How can the two sides of the brain be unequal from birth, yet have equal *potential*? A growth gradient, or perhaps several gradients, seemed to provide a natural resolution. We drew a parallel with *situs inversus*, in which the heart and other internal organs may develop with reversed asymmetry following certain interventions, and also with reversed asymmetry of the cerebral control of singing in passerine birds. Both phenomena suggest a simple gradient which, if reversed, results in a reversal of complex structural and functional asymmetries.

Since we wrote, however, there has been continuing debate as to whether the two sides of the brain do in fact possess equal potential for the mediation of language. On the basis of studies of hemidecorticates, Dennis (1980) has continued to claim that they do not, but her evidence has been challenged by Bishop (1983). In an exhaustive review and analysis of virtually all the published evidence on hemidicortication, St. James-Roberts (1981) has argued that age is not a significant factor in the recovery of linguistic functions following operation, but his analysis can also be challenged (Corballis 1983).

The current zeitgeist seems to favor a rigid, structuralist view of cerebral asymmetry, in which it is implied that only the left hemispheres of humans can mediate true language. This has led to an exaggeration of slight and subtle interhemispheric differences, and a neglect of those otherwise normal, linguistically competent individuals, including many left-handers, who do not display the usual pattern of cerebral lateralization (Corballis 1980b). The idea that lateralization might be controlled by one or more lateral growth gradients still seems to me to offer a more flexible and realistic approach, and it is pleasing to learn that it is not without pedigree.

McManus points out that there is still a sense in which the dictum that the genes are "left–right agnosic" must be true: A linear, sequential code could not of itself distinguish between enantiomorphs. There must be some extragenetic source of positional information involving a three-dimensional analogue map, which must itself be distinct from its own enantiomorph (i.e. it must not be bilaterally symmetrical). Possibilities as to the nature of left–right information, McManus's "signpost," are discussed by Wolpert (1978) and Bateson (1980).

Morgan and I implied a stronger sense in which the genes might be considered left–right agnosic: We suggested that genes could control only the presence or absence of an asymmetry, but not its direction. The data on the inheritance of handedness and of visceral *situs* seem to conform to this. Both require only two alleles, one that "reads the signpost" and so gives rise to the characteristic asymmetry and another that allows only chance variations in direction of asymmetry. Here, we are in agreement with **McManus.**

McManus suggests, however, that there might also be an allele that reverses the direction of the signpost, so that there *can* be genetic control over the direction of an asymmetry. Policansky's (1982b) data on asymmetry in flatfish seem to require the postulation of alleles coding opposite directions. To postulate *three* alleles, one coding dextrality (D), one sinistrality (S), and one chance (C), seems a little wanting in parsimony, but may well be necessary.

In McManus and Mascie-Taylor's (1979) analysis of the inheritance of asymmetrical handclasping, the data *within* populations are well described by two-allele models. The need to invoke three alleles is apparent only if one compares across populations. The most striking difference is between studies of Japanese samples, yielding high D and S frequencies but trivial C frequencies, and non-Japanese samples where C frequencies were typically high and only one of D or S yielded nontrivial frequencies. It is ironic that it should be the Japanese data that force the three-allele model for it was with the Japanese flatfish that the trouble began. Whence came the inscrutable vortex behind this mischief? Fishin' or fission?

How one fits genetic models depends upon one's initial assumptions, and **McManus**'s initial premises differ from those of Annett (1978) and myself (Corballis 1980a). McManus assumes no environmental influence but variable penetrance, whereas Annett and I have fit models to the inheritance of handedness assuming total penetrance but some degree of environmental influence. I do not know how the fit to the data on handclasping might be altered if one allowed an environmental component, or whether it would still be necessary to postulate three alleles.

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