Psychological Medicine

I. C. McManus

Handedness, language dominance and aphasia: a genetic model

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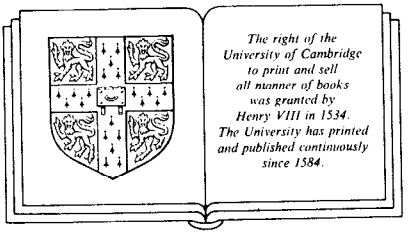

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SYNOPSIS A simple two-allele Mendelian model of the genetics of handedness is described and fitted to data in the literature. The model proposes that there are two alleles, D (dextral) and C (chance), the homozygous DD genotype producing only right-handers (directional asymmetry), the homozygous CC genotype producing a racemic mixture of 50% right-handers and 50% left-handers (fluctuating asymmetry), and the heterozygote, DC, being intermediate between the homozygotes and producing 25% left-handers, and 75% right-handers. It is also suggested that the true population incidence of left-handedness is 7·75%, deviations from this figure being due to either criterion shifts or selection biases. The same model is then fitted, by means of a number of minor conceptual extensions, to data from the literature on the relationship of handedness to language dominance, acute and permanent aphasia, and visual processing dominance.

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1. INTRODUCTION

The majority of humans show a preference for the use of the right hand rather than the left hand for skilled tasks such as writing, and a similar majority show evidence for the preferential localization of language functions in the left hemisphere, the two phenomena showing a moderate correlation. The causes of these asymmetries are not clear, and several explanations have been proposed, from purely environmental to purely genetic (see reviews by Harris, 1980; Corballis & Beale, 1976). This study presents a genetic model of handedness, of language dominance and of aphasia due to cerebral damage. The model for handedness will be described first, since it is independent of the validity of the models for language dominance and aphasia; in contrast, the models for language dominance and aphasia are closely interdependent upon the validity of each other, and of the model for handedness.

2. THE REQUIREMENTS OF A MODEL OF HANDEDNESS

Any model of handedness, be it genetic or environmental, has to meet certain minimal requirements:

(i) It must account for the data in the literature showing a familial trend in handedness. Left-handers represent about 10% of the children of two right-handed parents, 20–25% of the children of one right- and one left-handed parent, and about 40% of the children of two left-handed parents (see Tables 2 and 3 for further details).

(ii) It must explain the apparently high proportion of monozygotic twin pairs discordant for handedness (that is, in which one twin is right-handed and the other is left-handed), which has lead a number of research workers to conclude that handedness can have no genetic basis.

(iii) It must be able to account for the differences in incidence of handedness between different populations and, within studies, between generations.

(iv) The model should be compatible with the known inheritance of other biological asymmetries – for example, *situs* (the laterality of the viscera), and hand-clasping and arm-folding (McManus & Mascie-Taylor, 1979).

(v) The model must be biologically convincing. Morgan (1976) has pointed out that a genetic model may be fitted to any data as long as sufficient allelic pairs of varying penetrance at different loci are postulated.

3. THE PHENOTYPIC STRUCTURE OF HANDEDNESS

Genetic models are closely dependent upon supposed phenotypes. Elsewhere (McManus, 1979), I have considered the structure of handedness, as assessed by questionnaires, in some detail, and shall here discuss only the salient points. An assessment of large numbers of questionnaires suggested that handedness is distributed as a bimodal normal distribution, the two modes being situated symmetrically about zero (i.e. no preference for either hand), and there being little overlap of the distributions. In describing handedness we must therefore consider two distinct factors: the *direction* of handedness (i.e. right or left) and the *degree* of handedness (i.e. given that a person is right- or left-handed, how right-or left-handed are they, on a scale

Table 1. *The correlation of the degree of handedness of the propositus with the degree of parental handedness within direction of handedness groups*

Handedness				Multiple correlation propositus on parents	Significance	Simple correlation with propositus		Simple correlation of mother and father
Propositus	Mother	Father	*N*			Mother	Father	
R	R	R	308	0·0743	NS	0·0182	0·0718	−0·0142
L	R	R	43	0·2144	NS	−0·1660	0·1320	0·0159
R	R	L	26	0·1979	NS	0·0232	0·1979	0·0994
L	R	L	10	0·2944	NS	0·1386	−0·1366	0·5620
R	L	R	28	0·2280	NS	−0·1198	−0·1859	−0·1420
L	L	R	15	0·2696	NS	−0·1940	−0·1940	0·0763

from totally ambidextrous to completely lateralized). The detailed statistical analysis of such problems has been considered in detail elsewhere (McManus, 1983*a*). In the case of handedness the analysis is simplified since the compound, bimodal distribution readily separates into two separate normal distributions, and one may therefore ask whether either the direction or the degree of handedness is inherited. It must be noted that simply to calculate an overall correlation between the parental laterality index and the progeny laterality index is to confound both items, and to produce an uninterpretable result. Many previous studies have found incontrovertible evidence of familial trends in the direction of lateralization (see below). Table 1 shows the correlation of the progeny degree of handedness with the parental degree of handedness, as described in my previous study (McManus, 1979) in which 511 families (two parents and child) completed handedness questionnaires. There is no evidence *within groups* of the same direction of handedness, of familial resemblance in the degree of handedness, or any evidence of assortative mating for the degree of handedness.

As a result of this finding we need to search only for a genetic model of the *direction* of handedness, ignoring for our present purposes differences in the degree of handedness as assessed by questionnaire. Leiber & Axelrod (1981) have also found similar results.

4. THE BIOLOGICAL BACKGROUND

Before describing the present genetic model of handedness it is necessary to discuss the biological nature of asymmetry. Most previous models have failed to consider this point adequately and, I would argue, as perhaps would Corballis & Morgan (1978), have been misled as a result.

In discussing the biology of asymmetry we must distinguish clearly between *fluctuating asymmetry* and *directional asymmetry*.

5. FLUCTUATING ASYMMETRY

Biological and physical systems inevitably contain noise; molecules buffet against one another in quantal jumps according to the stochastic laws of thermodynamics. The result is that any system which is initially symmetrical will ultimately show some degree of asymmetry simply as the result of chance accumulation of noise. (Note that this is independent of any fundamental sub-atomic asymmetry.) These asymmetries will show a symmetric distribution about a mean of zero.

During early embryonic development small numbers of cells are involved and thus the relative role of chance variations becomes much larger. As a result of what Waddington (1957) has called 'canalization', such asymmetries are liable to become fixed, and may result in the relatively large asymmetries of adulthood (larger, that is, than might be expected on a purely chance basis). The net result of such chance or fluctuating asymmetries is that 50% of a population will tend to have one side 'dominant' (of whatever organ, tissue, or function is being considered), and the rest of the individuals will have the opposite side 'dominant'; this is equivalent to a chemist's racemic mixture of stereo-isomers. Fluctuating asymmetry may be demonstrated experimentally, and is usually investigated in the teeth or dermatoglyphics, both systems becoming fixed early in embryonic life. Events increasing the

level of 'biological noise' during early foetal development, such as heat (Siegel *et al.* 1977), audiogenic stress (Siegel & Smookler, 1973), and behavioural stress (Siegel & Doyle, 1975), result in greater degrees of fluctuating asymmetry (measured as increased variance, the mean remaining zero).

An important point about fluctuating asymmetry is that *none* of its variance can ever be genetically controlled (hence the name: the asymmetry fluctuates randomly from generation to generation).

6. DIRECTIONAL ASYMMETRY

Fluctuating asymmetry is undoubtedly (and inevitably) a common event during ontogeny. Nevertheless, on its own it cannot account for any of the asymmetries which are of interest to the psychologist or biologist – that is, asymmetries in which the mean of the distribution of (L–R) is not zero (or in the case of unilateral conditions, p(L) is not equal to p(R)); such conditions are said to show *directional asymmetry*.

Directional asymmetry differs biologically from fluctuating asymmetry. Its greater importance is suggested by the fact that in its extreme forms we do not even question its occurrence. Why the heart is on the left is neither a simple nor a trivial question. If the heart were on the left in 50% of cases then the answer might be simple – that fluctuating asymmetry followed by canalization inevitably produced it that way. Using a physical metaphor, to maintain an asymmetry we must search for a stabilizing force, for otherwise the system would inevitably return to symmetry; or rather, a directional asymmetry would return to a fluctuating asymmetry.

While directional asymmetry can (and one might argue, must) have some form of genetic control, there is an important limitation upon such control. Morgan (1976) has argued that it is, in principle, unlikely that a gene carries direct information about chirality – that is, paired alleles have not been shown, in any convincing case, to produce enantiomorphic phenotypes in their carriers. Thus, if one homozygote of an allelic pair produces one particular directional asymmetry, then the other homozygote cannot produce the mirror-image directional asymmetry (although see McManus & Mascie-Taylor (1979) for further discussion of this point). The present model relies heavily upon Morgan's principle for its origins, although not, of course, for its justification as a satisfactory fit to the data.

The inter-relation of directional and fluctuating asymmetry may be seen in a series of morphological examples.

In most vertebrates the heart and stomach are on the left and the liver is on the right. This situation (*situs solitus*) (SS) is occasionally mirror-reversed to give *situs inversus* (SI). Spemann & Falkenberg (1919) found that tying a fine thread around the mid-line of a developing newt embryo produced conjoined twins. The left-hand member of the pair almost always showed SS, and the right-hand member showed SI in about half of the cases. A similar situation exists if the embryo is completely split in two (Ruud & Spemann, 1923). Analogous findings have been reported in conjoined trout (Lynn, 1946). In other animals SI has been shown to be produced teratogenically (Shehenfelt, 1974), by cold (Newman, 1925), or by irradiation (Wilson *et al.* 1953), but in no case does the incidence rise above 50%.

The *iv* mutation in the mouse, when homozygous, produces SI in exactly 50% of cases (Layton, 1976). Nevertheless, the *iv* gene shows *complete* penetrance. When two *iv* homozygotes are mated then the progeny show 50% of SI, irrespective of the particular phenotype of the parents. A similar situation exists in another mouse mutation (Tihen *et al.* 1948), producing SI, and also in the platyfish *Xiphorus maculatus* (Baker-Cohen, 1961). In man, Kartagener's syndrome of chronic sinusitus, bronchiectasis and situs inversus, is inherited as an autosomal recessive, with the limitation that only 50% of homozygotes show the SI component of the syndrome (Afzelius, 1976). Among human monozygotic twins showing situs inversus, 46% of 13 reported pairs are concordant and the rest are discordant (Lowe & McKeown, 1953); the expected values are 33·3% concordant and 66·6% discordant, under a model identical to that for the *iv* mutation.

Directional and fluctuating asymmetry can also be seen in the arrangement of the optic chiasma in the flatfish, the *Heterosomata* (McManus & Mascie-Taylor, 1979).

A behavioural example of fluctuating asymmetry is given by Collins (1970), who studied the pawedness of mice which had been inbred for 28

generations (and hence we may assume were almost certainly homozygous at all loci). Of these animals 50% were left-pawed and 50% were right-pawed, with no evidence of any inheritance over a further three generations (Collins, 1970).

7. PREVIOUS GENETIC MODELS OF HANDEDNESS

A number of previous genetic models of handedness have been proposed, and reviews may be found elsewhere (Corballis & Beale, 1976; Corballis, 1980). In summary, all these models have defects in fitting the available data (Corballis, 1980). This defect, I would argue, is primarily due to their failure to consider the biological basis of asymmetry. In particular, they contravene what I have called 'Morgan's principle' that paired alleles do not produce enantiomorphic phenotypes. Thus the models of Ramaley (1913), Rife (1950), Trankell (1955), Annett (1964) and Levy & Nagylaki (1972) all propose such alleles. The only exception is Annett's second model (1978), in which one allele 'produces' fluctuating asymmetry. Annett's model fails, however, in that it requires different parameters for singletons and twins (Annett, 1978), which is biologically implausible, particularly given that there is no adequate evidence for twins differing from singletons in their handedness (McManus, 1980). Corballis (1980) has also rejected Annett's model on other grounds. Nevertheless, Annett's model has close similarities to my own model, and I would suggest that its failure is not due to an inappropriate biological basis, but rather due to its assumption of an implausible phenotypic description of handedness, with its emphasis upon a single normal distribution. The question will be considered in more detail below.

8. THE MODEL

As stated earlier, the present model is based explicitly upon the information described in 'The biological background' (section 4 above). It is proposed that there are two alleles, D and C. Allele D (for dextral), produces 100% right-handers when it is homozygous. Allele C (for chance) 'produces', in its homozygous form, pure fluctuating asymmetry (i.e. there is no control over the phenotypes of the progeny). Thus, *exactly* 50% of the CC genotype are right-handed, and 50% are left-handed. In this case, 50% is not an arbitrary figure (45% or 23%, for example, could not be fitted to the same argument), but is a *precise* statement of a particular genetic manifestation. Also, it must be emphasized that, although only 50% of CC individuals are left-handed, this does *not* mean that the CC genotype is only partially penetrant. It shows 100% penetrance for its real phenotype, which is fluctuating asymmetry, and hence, as a secondary consequence, produces only 50% of left-handers.

Thus far, the model can be defined *a priori* from a knowledge of the biology of asymmetry. The next step is less predictable. The problem is that the proportion of left-handers to be expected from the heterozygote, DC, is undefined. If C is recessive (i.e. the heterozygote manifests as the commoner of the two homozygotes) then one would expect 100% right-handers from the DC genotype. Conversely, if C is dominant (i.e. the heterozygote acts as the less common of the two homozygotes) then one would expect 50% of left-handers from the heterozygote. But, of course, there could also be an infinity of intermediate positions in which the heterozygote produces a proportion, $p(\mathrm{L}|\mathrm{DC})$, of left-handers, where $p(\mathrm{L}|\mathrm{DC})$ is between 0 and 0·5. In particular, I wish to call the position exactly intermediate between the two extremes 'additive'. The additive DC genotype thus produces 25% left-handers and 75% right-handers. Whatever the particular value of $p(\mathrm{L}|\mathrm{DC})$, the use of values other than 0 or 1 may be seen as examples of the 'random phenotype concept' (Birnbaum, 1972).

The models to be discussed are thus a restricted set of those called model I in McManus & Mascie-Taylor (1979).

Genotype	p(left-hander|genotype)	p(right-hander|genotype)
DD	0·0	1·0
DC	$p(\mathrm{L}\|\mathrm{DC})$	$1{\cdot}0-p(\mathrm{L}\|\mathrm{DC})$
CC	0·5	0·5

The parameter $p(\mathrm{L}|\mathrm{DC})$ controls the degree of dominance of the heterozygote. Thus,

if $p(\mathrm{L}|\mathrm{DC}) = 0{\cdot}5$ then C is recessive;
if $p(\mathrm{L}|\mathrm{DC}) = 0$ then C is dominant;
if $p(\mathrm{L}|\mathrm{DC}) = 0{\cdot}25$ then C is 'additive'.

Note that pL|DC) cannot be greater than 0·5 if the model is to satisfy the biological requirements mentioned earlier. In the rest of this study I shall suggest that the evidence best supports the view that $p(L|DC) = 0{\cdot}25$, and hence the genetic model is 'additive'.

9. THE PROBLEM OF DIFFERENT INCIDENCES OF LEFT-HANDEDNESS BETWEEN AND WITHIN STUDIES

As mentioned earlier, the manifest incidence of left-handedness varies, both between different studies and between generations within particular studies. These differences in incidence represent a major problem for any model of left-handedness. One can hardly make the usual assumption of classical genetics, that all differences in incidence are due to differences in allele frequencies, since it is clear that, by using different definitions of left-handedness, the same study may be used to produce different progeny incidences of left-handedness. Clearly, in such a case it would be absurd to argue that the allele frequencies had also changed. There are two approaches to the problem. We may follow Levy & Nagylaki (1972) and Levy (1977) who argue that data are invalid for genetic analysis unless the parental incidence of sinistrality is equal to the progeny incidence of sinistrality. That process of exclusion left them with only a single set of data, that of Rife (1950). They still, however, make the assumption that Rife's criterion is the *correct* one; if one cared to dispute Rife's definition of handedness one would be left with absolutely no data at all with which to test a model. This position seems somewhat unsatisfactory. The alternative position, adopted by Annett (1978), seems far more realistic. In the first instance, one assumes that all studies have the same *allelic* proportions, and hence have the same proportions of the true phenotypes (i.e. in her case, RS+ and RS−). Differences in apparent proportions of sinistrality are then due to differences in *criterion* or *threshold* of left-handedness. As she points out (Annett, 1978), this has a close similarity to the methodology of signal detection theory where, despite differences in response bias (Beta), one is trying to find a true sensitivity (d'). In the following analysis I shall follow Annett in attempting to make corrections for differences in the incidence of left-handedness, and thus shall attempt to fit *all* the available data. My actual calculations for these corrections will, however, be somewhat different from those of Annett.

Let $p(L_m)$ be the *manifest* proportion of left-handers in a particular population; thus $p(L_m)$ can vary between populations, or even within a population if the criterion for left-handedness should be changed. In contrast, let $p(L_t)$ be the *true* incidence of left-handedness, which I would propose, at least in the first instance, is constant in all the different populations being studied. Clearly, while $p(L_m)$ can be directly estimated from the data, the value of $p(L_t)$ may only be hypothesized.

Given a particular pair of values of p(L|DC) and $p(L_t)$, one obtains predictions which are the same for all data sets. Clearly, these must be modified for each particular data set, from a knowledge of $p(L_m)$. To do this requires assumptions about the processes involved in altering the value of $p(L_t)$ to that of $p(L_m)$. There are two major ways in which $p(L_m)$ may not equal $p(L_t)$.

(i) A different criterion of left-handedness may be used ('criterion shift').

(ii) There may be a response bias, whereby left-handers tend not to respond to questionnaires (as perhaps may have been true at the turn of the century) or they tend to over-respond to questionnaires (as may well be true now).

Of course, separate corrections must be made for both the parental and progeny generations ($p(L_t)$ for parents being assumed to be equal to $p(L_t)$ for the progeny, although $p(L_m)_{par}$ need not be equal to $p(L_m)_{prog}$).

An examination of the studies in the literature suggests that in all parental cases, and almost all of the progeny cases, criterion shifts cannot be eliminated. But, similarly, in most surveys response bias cannot be eliminated either. Exceptions are my own surveys, in which I am forced to argue that the correct criterion of left-handedness has been used, and the study of Mascie-Taylor (see below) who, I would also argue, has used the correct criterion, and in whose study there was probably no response bias since there was almost 100% ascertainment. It is noteworthy that in Mascie-Taylor's study the parental and progeny incidences are equal, and the incidence of sinistrality is close to that which I shall later hypothesize. Elsewhere (McManus,

Table 2. *The results of* 12 *studies of the frequency of right- and left-handed progeny from R × R, R × L and L × L matings*

	$p(L_m)$ Progeny	$p(L_m)$ Parents	R × R		R × L		L × L		
			R	L	R	L	R	L	χ^2_L† (df = 1)
Ramaley (1913)	0·1556	0·0803	841 (822·8)	115 (133·2)	113 (126·8)	54 (40·2)	1 (5·3)	7 (2·7)	18·725***
Chamberlain (1928)	0·0477	0·0356	6917 (6915·0)	308 (310·0)	411 (412·8)	53 (51·2)	18 (20·6)	7 (4·4)	1·666
Rife (1940)	0·0877	0·0524	1842 (1941·2)	151 (151·8)	140 (141·6)	34 (32·4)	5 (7·7)	6 (3·3)	3·042
Merrell (1957)	0·2362	0·1553	140 (135·5)	34 (38·5)	33 (38·8)	20 (14·2)	8 (6·8)	2 (3·2)	14·266***
Annett (1973)	0·1063	0·0440	6206 (6208·9)	669 (666·1)	471 (474·5)	125 (121·5)	5 (4·1)	1 (1·9)	0·792
Ferronato *et al.* (1974)	0·0976	0·0986	154 (151·8)	11 (13·2)	31 (33·3)	9 (6·7)	0 (0·0)	0 (0·0)	1·285
Mascie-Taylor (unpublished)	0·0831	0·0930	232 (232·7)	17 (16·3)	41 (40·3)	7 (7·7)	3 (3·0)	1 (1·0)	0·109
Chaurasia & Goswani (unpublished)	0·1407	0·1040	1060 (1054·5)	144 (149·5)	122 (133·8)	46 (34·2)	3 (5·0)	4 (2·0)	7·498**
Annett (1978)	0·0850	0·0547	1656 (1655·8)	130 (130·2)	170 (171·4)	40 (38·6)	4 (2·8)	0 (1·2)	2·855
Carter-Saltzmann (1980)	0·1320	0·0760	303 (300·7)	37 (39·3)	45 (46·6)	15 (13·4)	0 (0·0)	0 (0·0)	0·399
Coren & Porac (1980)	0·1838	0·0838	315 (319·5)	68 (64·5)	57 (53·9)	16 (19·1)	0 (0·0)	0 (0·0)	0·931
McGee & Cozad (1980)	0·2457	0·1802	848 (914·2)	211 (244·8)	325 (346·1)	150 (128·9)	30 (35·8)	22 (16·2)	13·718***

The numbers in parentheses are fitted values.
† $p(L_t) = 0·0775$; $p(L|DC) = 0·25$.
**$P < 0·01$; ***$P < 0·001$.

Table 3. *The numbers of families with particular numbers of left-handed children by family size and parental handedness for 4 separate data sets*

Data set	No. (children)	R×R Left-handers						R×L Left-handers						L×L Left-handers						Likelihood ratio†
		0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	
ICM1 (propositi)	1	58	9	—	—	—	—	14	5	—	—	—	—	0	0	—	—	—	—	$\chi^2_L = 40{\cdot}219$, df = 44
		(58·1)	(8·9)					(14·9)	(4·1)											
	2	211	57	3	—	—	—	35	16	5	—	—	—	0	0	1	—	—	—	
		(205·1)	(59·6)	(6·3)				(34·9)	(18·2)	(2·9)				(0·50)	(0·40)	(0·10)				
	3	123	63	6	0	—	—	22	24	6	1	—	—	2	1	1	0	—	—	
		(127·7)	(52·8)	(10·5)	(0·97)			(26·4)	(19·7)	(6·1)	(0·77)			(1·5)	(1·7)	(0·76)	(0·13)			
	4	70	39	6	1	0	—	8	8	7	1	0	—	0	0	1	0	0	—	
		(68·2)	(35·9)	(19·1)	(1·8)	(0·15)		(9·7)	(9·2)	(4·1)	(0·98)	(0·10)		(0·27)	(0·39)	(0·25)	(0·08)	(0·01)		
	5	9	12	6	2	0	0	1	0	0	1	0	0	1	0	0	0	0	0	
		(15·1)	(9·5)	(3·4)	(0·83)	(0·13)	(0·01)	(0·66)	(0·74)	(0·42)	(0·14)	(0·03)	(0·00)	(0·20)	(0·34)	(0·28)	(0·14)	(0·04)	(0·00)	
ICM2 (propositi)	1	134	15	—	—	—	—	17	9	—	—	—	—	1	0	—	—	—	—	$\chi^2_L = 37{\cdot}787$, df = 27
		(131·4)	(17·6)					(20·8)	(7·2)					(0·70)	(0·28)					
	2	91	22	2	—	—	—	19	3	3	—	—	—	0	0	0	—	—	—	
		(90·1)	(22·7)	(2·3)				(16·2)	(7·6)	(1·2)										
	3	22	7	0	2	—	—	6	11	3	0	—	—	0	0	0	0	—	—	
		(21·7)	(7·7)	(1·4)	(0·13)			(10·6)	(7·1)	(2·1)	(0·25)									
	4	10	5	0	0	0	—	3	1	0	0	0	—	1	0	0	0	0		
		(9·4)	(4·2)	(1·1)	(0·19)	(0·02)		(1·8)	(1·5)	(0·61)	(0·14)	(0·01)		(0·30)	(0·39)	(0·23)	(0·07)	(0·01)		
	5	4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	
		(2·3)	(1·2)	(0·40)	(0·10)	(0·01)	(0·00)													
ICM2 (maternal family)	1	74	4	—	—	—	—	6	2	—	—	—	—	0	0	—	—	—	—	$\chi^2_L = 24{\cdot}962$, df = 28
		(72·0)	(6·0)					(6·5)	(1·5)											
	2	107	18	3	—	—	—	11	3	0	—	—	—	2	0	0	—	—	—	
		(110·0)	(16·4)	(1·6)				(9·3)	(4·1)	(0·57)				(1·0)	(0·82)	(0·18)				
	3	81	16	4	0	—	—	16	1	0	2	—	—	0	0	0	0	—	—	
		(81·4)	(16·3)	(3·1)	(0·27)			(10·5)	(6·6)	(1·7)	(0·19)									
	4	31	10	1	0	0	—	0	0	0	2	0	—	0	0	0	0	0	—	
		(31·9)	(7·7)	(2·1)	(0·34)	(0·03)		(0·91)	(0·74)	(0·28)	(0·06)	(0·01)								
	5	19	7	1	1	0	0	3	2	0	0	0	0	0	0	0	0	0	—	
		(20·2)	(5·5)	(1·8)	(0·44)	(0·07)	(0·01)	(1·9)	(1·9)	(0·89)	(0·26)	(0·05)	(0·00)							
ICM2 (paternal family)	1	86	4	—	—	—	—	8	1	—	—	—	—	0	0	—	—	—	—	$\chi^2_L = 26{\cdot}501$, df = 34
		(83·3)	(6·7)					(7·3)	(1·7)											
	2	100	27	0	—	—	—	7	5	0	—	—	—	0	1	0	—	—	—	
		(109·6)	(15·8)	(1·6)				(8·0)	(3·5)	(0·48)				(0·50)	(0·41)	(0·09)				
	3	65	11	2	0	—	—	4	3	2	0	—	—	0	1	0	0	—	—	
		(63·3)	(12·2)	(2·4)	(0·21)			(5·0)	(3·1)	(0·80)	(0·09)			(0·36)	(0·43)	(0·18)	(0·03)			
	4	39	11	2	0	0	—	2	1	0	0	0	—	0	0	0	0	0	—	
		(39·9)	(9·1)	(2·5)	(0·42)	(0·03)		(1·4)	(1·1)	(0·41)	(0·9)	(0·01)								
	5	13	9	1	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	
		(16·8)	(4·3)	(1·5)	(0·35)	(0·05)	(0·00)	(0·39)	(0·37)	(0·18)	(0·05)	(0·01)	(0·00)							

The values in parentheses are the expected values for a model with $p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.
† $p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

1979), I have given details of the calculations using both methods, and suggest that in most cases they give sufficiently similar results to mean that they cannot, for most practical purposes, be differentiated. I have therefore, for simplicity, assumed that all differences in the incidence of $p(L_m)$ are due to criterion shifts alone; the detailed mathematics is given in the Appendix.

Clearly, in applying the corrections for a criterion shift one is assuming that two separate processes are occurring simultaneously:

(*a*) some true right-handers are manifesting as left-handers, and

(*b*) some true left-handers are manifesting as right-handers.

Without further data, it is not possible to discriminate between these two processes. In order to carry out the calculations I have therefore assumed that, if the manifest incidence of left-handedness is less than the true incidence, then this is entirely due to true left-handers manifesting as right-handers (i.e. there are *no* true right-handers manifesting as left-handers); and vice versa for $p(L_m)$.

Given these assumptions, it is possible to fit the genetic model, and hence to estimate $p(L_t)$, $p(L|DC)$ and the goodness of fit of the model.

10. FAMILIAL DATA

In fitting the model I have used the results of ten studies of the incidence of left-handedness in the progeny of R × R, R × L and L × L matings (Ramaley, 1913; Chamberlain, 1928; Rife, 1950; Merrell, 1957; Annett, 1973; Ferronato *et al.* 1974; Annett, 1978; Carter-Saltzmann, 1980; McGee & Cozad, 1980; Coren & Porac, 1980). In using these data sets certain modifications have been made. The data of Chamberlain (1928) have been used as quoted by Annett (1973), notwithstanding the trivial inconsistencies demonstrated by Levy (1977). In using the Chamberlain data I have considered only those individuals obtained by random sampling, since the incidence of left-handedness is higher among those families obtained by special appeal ($\chi^2 = 3{\cdot}43$, df = 1, $P < 0{\cdot}10$), and thus one suspects a response bias. Similar considerations for the data of Annett (1973) mean that only the randomly obtained data have been included. The data of Hubbard (1971) have not been used, since R × L and L × L matings were not distinguished. It was not possible to use the data of Falek (1959), since the sample was incomplete and there was no indication of the overall incidence of left-handedness in the propositus generation.

As well as the above published studies, I was also able to use the results of two unpublished studies. Dr Mascie-Taylor, of the Department of Physical Anthropology, University of Cambridge, allowed me to use data from a survey carried out by him in 1977 in a Cambridge suburb; other aspects of this study have been reported elsewhere (Mascie-Taylor, 1980, 1981; Mascie-Taylor & Gibson, 1978, 1979). The data were obtained from a comprehensive study of a population, there being almost no failures to respond, handedness being assessed directly by the research worker, and sampling being truly random. Drs Chaurasia and Goswami, of the School of Biological Sciences, Bhopal University, India, have allowed me to quote data they obtained from a questionnaire distributed to a large number of their students. Results from these studies are presented in Table 2.

It should be noted that most of the above studies ignore family size, all the children from a particular family being combined. Thus, if a single R × R pair produced one right- and one left-handed child these two individuals are entered *once into column* R *and once into* column L. However, these individuals cannot be regarded as strictly independent entries in Table 2. In view of the ubiquity of this phenomenon I have analysed the data as if they came from independent single-child families. The data from my own studies (below) do not suffer from this problem. These data are shown in Table 3, and have been reported in more detail elsewhere (McManus, 1979).

It should be remembered that the effect of treating several individuals from a single family as if they were individuals from independent families will not bias estimates of the parameters of the model (at least, as long as the selection of these families is unbiased), but rather will increase the apparent sample size above the true sample size, and hence cause there to be lower standard errors of the parameters than are valid. As a result, data sets will apparently fail to fit the overall model when their fit may truly be adequate – i.e. rejection of fit becomes more liberal than it should be. This point will be discussed later.

The data of survey 1 were obtained by questionnaires given to undergraduates at the

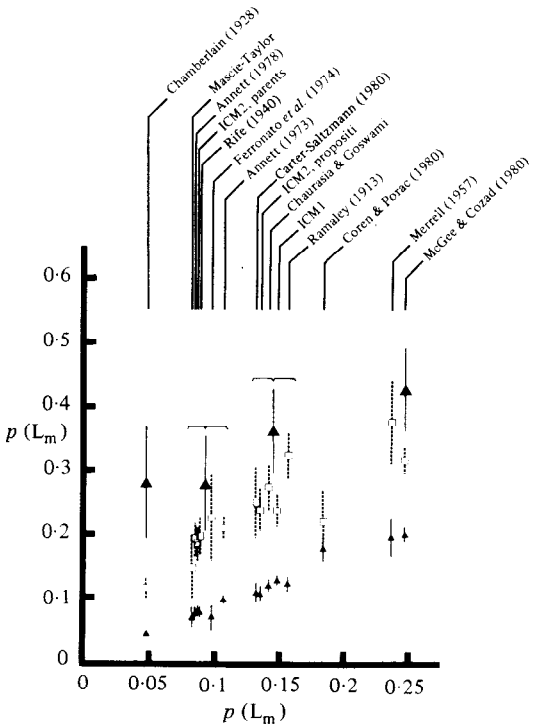

FIG. 1. The results of 15 family studies of the inheritance of handedness. The abscissa shows the manifest incidence of handedness in all progeny in the study, and the ordinate shows the manifest incidence of handedness in the progeny of particular parental combinations: R × R (▲), R × L (including L × R) (□), and L × L (▲). Points are plotted ± one standard error.

University of Cambridge in May 1977; the students were asked to provide information on their handedness and on the handedness of their siblings, parents and grandparents (it was stressed to them that it was preferable not to reply to a question rather than to guess at an answer). Handedness was classified on the basis of writing hand, with the single exception that those right-handed writers who originally wrote with their left hand, but had been forced to write with their right hand, were classified as left-handed. The data for the propositus and the siblings of the propositus were classified according to parental handedness (data set ICM1: Table 3). The response rate to the questionnaire was difficult to assess accurately but was of the order of 50%. The second study, survey 2, was carried out in June 1977, and the questionnaire was given to all Cambridge graduates who were collecting their degrees in person. The questionnaires were distributed on the eve of the graduation ceremony. Information was thus obtained not only from the students, but also from other members of the students' families, so that information could be obtained on the handedness of parents, parents' siblings and grandparents, as well as on the students' siblings. Once more, it was emphasized that questions should be answered only if the answer

Table 4. *Evidence from* 19 *studies for assortative mating for handedness*

Study	$p(L_m)$ (%)	N	R × R	R × L	L × L	χ^2_L (df = 1)	Direction†
ICM2 (grandparents)	3·21	497	465	32	0	1·06	−
Chamberlain (1928)	3·55	2177	2031	137	9	9·89**	+
Annett (1973)	4·06	2151	1978	171	2	0·87	−
ICM2 (parents)	4·48	837	766	67	4	2·61	+
Rife (1940)	5·24	687	620	62	5	4·12*	+
ICM1 (parents)	6·66	195	172	20	3	4·01*	+
Carter-Saltzmann (1980) (biological parents)	7·56	205	175	29	1	0·03	−
Carter-Saltzmann (1980) (adoptive parents)	8·04	286	244	38	4	2·34	+
Mascie-Taylor (unpublished)	8·03	193	163	29	1	0·06	−
Ramaley (1913)	8·03	305	258	45	2	0·00	+
Leiber & Axelrod (1981)	8·11	2257	1902	344	11	1·27	−
Coren & Porac (1980)	8·39	459	384	73	2	0·63	−
Hicks & Kinsbourne (1976) (biological parents)	9·35	1101	923	150	28	31·13***	+
ICM1 (propositi)	9·68	418	337	81	0	8·71**	−
ICM2 (propositi)	9·81	433	351	79	3	0·40	−
Ferronato *et al.* (1974)	9·86	76	61	15	0	1·65	−
Merrell (1957)	15·53	103	75	24	4	1·16	+
McGee & Cozad (1980)	18·21	615	413	180	22	0·19	+
Hicks & Kinsbourne (1976) (step-parents)	31·94	108	54	39	15	3·03	+

† −, Excess of R × L (negative assortative mating); +, Deficit of R × L (positive assortative mating).
*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$.

Table 5. *The observed numbers of R–R, R–L and L–L pairs of MZ and DZ twins from 13 different studies*

Study	MZ twins					DZ twins				
	$p(L_m)$	R–R	R–L	L–L	$\chi^2_L(df = 1)$	$p(L_m)$	R–R	R–L	L–L	$\chi^2_L(df = 1)$
Wilson & Jones (1932)	0·1071	56 (56·9)	13 (11·2)	1 (1·9)	0·771	0·1138	97 (97·5)	24 (23·0)	2 (2·5)	0·164
Stocks (1933)	0·0952	35 (35·0)	6 (5·9)	1 (1·0)	0·004	0·1063	76 (75·8)	16 (16·4)	2 (1·8)	0·037
Newman *et al.* (1937)	0·1900	34 (33·4)	13 (14·1)	3 (2·4)	0·225	0·1100	39 (40·0)	11 (9·0)	0 (1·0)	2·400
Bouterwek (1938)	0·1885	80 (81·9)	38 (34·2)	4 (5·9)	1·124	0·1714	23 (24·3)	12 (9·5)	0 (1·3)	3·205
Rife (1940)	0·1188	176 (176·5)	41 (40·0)	6 (6·5)	0·062	0·1541	104(105·5)	39 (36·1)	3 (4·5)	0·804
Thyss (1946)	0·1844	72 (69·8)	24 (28·3)	7 (4·8)	1·634	0·1627	60 (60·9)	24 (22·3)	2 (2·9)	0·432
Rife (1950)	0·1282	261 (265·7)	76 (66·6)	6 (10·7)	3·680	0·1161	164(166·4)	45 (40·1)	2 (4·4)	2·284
Dechaume (1957)	0·2424	19 (19·3)	12 (11·4)	2 (2·3)	0·079	0·1969	21 (21·5)	11 (10·0)	1 (1·5)	0·283
Zazzo (1960)	0·1332	199 (198·3)	51 (52·3)	9 (8·3)	0·088	0·1089	264(268·6)	69 (59·9)	2 (6·5)	5·726*
Carter-Saltzmann *et al.* (1976)	0·1711	132 (131·0)	46 (48·1)	9 (7·9)	0·237	0·1931	115(115·7)	54 (52·6)	7 (7·7)	0·099
Loehlin & Nichols (1976)	0·1410	380 (386·6)	123 (109·9)	11 (17·5)	4·408*	0·1111	261(265·6)	70 (60·7)	2 (6·6)	5·917*
Springer & Searleman (1978)	0·1667	53 (53·1)	19 (18·8)	3 (3·1)	0·006	0·1596	35 (33·5)	9 (12·0)	3 (1·5)	1·998
NCDS (unpublished)	0·1512	32 (31·6)	9 (9·8)	2 (1·6)	0·183	0·1477	66 (64·5)	18 (20·9)	4 (2·5)	1·181

The values in parentheses are the expected values for a model with $p(L_t) = 0·0775$; $p(L|DC) = 0·25$.
* $P < 0·05$.

was fairly certain, guessing being discouraged. Handedness was classified as in the previous study. From this study three separate sets of family data were obtained: students and students' siblings as a function of parental handedness (ICM2 propositus generation); and parental and parental siblings' handedness as a function of grandparental handedness (ICM2 parental generation), the data being analysed separately for the mother's family and the father's family. The response rate of this study was of the order of 20%.

Fig. 1 shows the data of Tables 2 and 3 plotted graphically, with the proportions of left-handed progeny of the three mating types shown as a function of the overall incidence of left-handedness among the progeny. Since L × L matings are rare, these have been combined for the purposes of clarity. It is apparent that there is a fairly clear relationship between the data from all the studies.

11. ASSORTATIVE MATING

The presence of assortative mating complicates the fitting of genetic models. It is easy to produce social theories which would predict either negative or positive assortative mating for handedness. Table 4 summarizes 19 data sets, and shows the likelihood ratio chi-squared goodness-of-fit statistic for the binomial distribution. Of the 19 data sets, 10 show a deficit of R × L pairs, and 9 show an excess. Several of the differences reach a conventional level of significance, but the presence of repeated significance testing means that some of these results are Type I errors. In summary, assortative mating need be of no consequence for the fitting of genetic models of handedness.

12. TWIN DATA

Elsewhere, I have summarized 19 different sets of twin data in the literature (McManus, 1980). Of these, there is evidence that those published up to 1930 are unreliable due to the inadequacy of the determination of zygosity, and I have not therefore fitted the model to them. I have also used the recent data of Springer & Searleman (1978), and some unpublished data from the National Child Development Study, other aspects of which concerning twins have been published elsewhere (Adams *et al.* 1976). Table 5 summarizes the available data from the 13 suitable studies.

Several claims have been made about handedness in twins:

(i) Monozygotic (MZ) twins show binomial proportions of R–R, R–L and L–L pairs (and hence that handedness cannot be under genetic control).

(ii) MZ twins have a higher incidence of sinistrality than do dizygotic (DZ) twins.

(iii) Twins in general have a higher incidence of sinistrality than do singletons.

I have critically reviewed evidence for these

statements elsewhere (McManus, 1980) and find that none of them is adequately supported by the data. This is important, since on the basis of (ii) and (iii) in particular, Nagylaki & Levy (1973) have argued that twins are not suitable for fitting to genetic models, since twins show increased pathological left-handedness and also, in MZ twins, 'ectodermal mirror-imaging'. Since there is no evidence for (ii) and (iii), genetic models should be able to cope with data from twins as well as those from singletons. In particular, as Corballis & Beale (1976) have pointed out, the model of Levy & Nagylaki cannot cope with these MZ twin data.

As with data from the singletons, so in the case of twins it is necessary to account for differences in the incidence of sinistrality between studies. Once more I shall assume, along with Annett, that the differences are due to variation in the threshold or criterion of left-handedness, and that in all studies the underlying allele frequencies are the same in each case. Unlike Annett, I shall assume that the phenotypes in twins are the same as in singletons.

13. METHOD OF FITTING THE GENETIC MODEL

In fitting the genetic model one has to obtain the best estimates of two parameters from the data ($p(L_t)$ and $p(L|DC)$) and to determine whether, at these best estimates, the model fits the observed data sufficiently well. A maximum likelihood method has been used to obtain best estimates and also to determine the goodness-of-fit of the model to the data. Maximum likelihood was preferred to chi-square goodness-of-fit testing, since in some cells of the data the numbers were relatively small (although chi-square fitting has been used elsewhere (McManus, 1979)).

In practice, the method of fitting consists of choosing a pair of (not necessarily best) values of $p(L_t)$ and $p(L|DC)$ and determining the support (log-likelihood) for that pair of values, given all the data of Tables 2, 3 and 5. In so doing, a value of $p(L_m)$ is required for each independent data set. Strictly, each value of $p(L_m)$ should also be estimated by a maximum likelihood method. However, in practice it is probable (although unproven) that the maximum likelihood estimates of the $p(L_m)$ values are those derived directly from the data sets themselves, and this has been assumed for present purposes. A value of $p(L_m)_{par}$ is also required for each independent set of family data and this also has been estimated directly from the data.

Two methods of finding the best estimates of $p(L_t)$ and $p(L|DC)$ have been used.

(i) The fit of the model to the data has been found for all combinations of values of $p(L_t)$ in the range 0·02 (0·0025) 0·20, and of $p(L|DC)$ in the range 0·0 (0·025) 0·5. This analysis showed that the likelihood function was relatively well-behaved.

(ii) As a result of the first analysis a quasi-Newton–Raphson iterative method was used to find the actual best estimates of the two parameters (Adby & Dempster, 1974).

Given a pair of estimates of $p(L_m)$ and $p(L|DC)$, one may ask how well this model fits a particular data set, or how well it fits the total data set. For the latter case one need only compare the support found with the theoretical support value to be expected from a 'perfect fit'. Twice this difference may be treated as a χ^2 statistic, with a number of degrees of freedom equal to the number of free parameters remaining in the model.

14. RESULTS OF FITTING THE GENETIC MODEL

Considering the whole of the data from Tables 2, 3 and 5, the maximum support of −11446·441 is found at estimates of $p(L_t)$ of 0·0767 and of $p(L|DC)$ of 0·2647 (model A). For these data a 'perfect fit' would give a support of −11330·736. The difference between these support values is equivalent to a χ^2 value of 231·41 with 169 degrees of freedom. This value of χ^2 is highly significant ($P < 0·005$). The model obtained is thus not adequate.

A problem with maximum likelihood methods of fitting statistical models is that they are very vulnerable to a few 'outliers' – data points which are, for one reason or another, in error. The χ^2 value obtained above suggested that it was worth searching for such points by fitting each data set separately. Tables 2, 3, and 5 contain columns showing χ^2 values for the fit of a model ($p(L_t) = 0·0775$; $p(L|DC) = 0·25$) to each of the individual data sets. Considering the individual sets of twins, none is individually significant at the $P < 0·01$ level, and the combined value of $\chi^2_{26} = 37·028$ is not significant at the 0·05 level. The twins are thus unlikely to include any

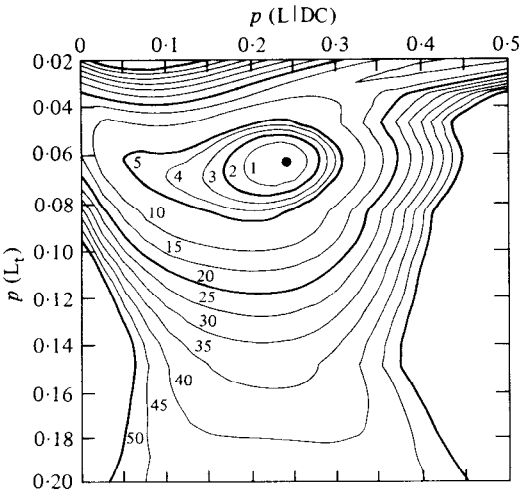

FIG. 2. A contour map of the goodness-of-fit of the present model to the reduced data set (i.e. model B, see text and also Table 8). The ordinate shows particular values of the hypothesized true incidence of left-handedness, and the abscissa shows particular values of the expression of the heterozygote, from 0 (C allele recessive) to 0·5 (C allele dominant), with additivity of the C allele occurring at 0·25. The contours represent differences of support (log-likelihood ratio) between the maximum likelihood fit (represented by the dot in the centre) and other combinations of parameters. Contours are plotted at 1, 2, 3, 4, 5, 10, 15, 20, 25, 30, 35, 40, 45 and 50 support units difference from the optimal fit. Contours at 2, 5, 20 and 50 units are plotted at double thickness. A support unit difference of 2 is approximately equivalent to a conventional 95% confidence limit.

'outliers'. Similarly, my own family data (Table 3) show no individual data sets with an inadequate fit, and the overall value $\chi^2_{133} = 129{\cdot}469$ is highly acceptable. In contrast, the data of Table 2 are not so acceptable. The overall value of $\chi^2_{12} = 65{\cdot}285$ is highly significant. Scrutiny of the individual goodness-of-fit values shows that this lack of fit is almost entirely due to the data sets of Chaurasia & Goswami, Ramaley, Merrell, and McGee & Cozad, each of which is individually significant with $P < 0{\cdot}01$ or less. As stated earlier, it is not strictly permissible to treat such data sets as if they contained a number of individual children from independent families, since in many cases sibships of more than one have been combined, and it is therefore not surprising that it is among these data sets that outliers have been found. After removal of these four data sets one obtains a satisfactory value of $\chi^2_8 = 11{\cdot}078$.

In view of the probability that the inadequate fit of model A was due to the poor fit to just four data sets, the process of calculation was repeated without them. This resulted in a second model (model B) in which the maximum support was $-9431{\cdot}723$ and the maximum likelihood estimates of the parameters were $p(L_t) = 0{\cdot}0642$ and $p(L|DC) = 0{\cdot}2329$. A 'perfect fit' would give a support of $-9345{\cdot}466$, and the difference between the observed and a perfect fit is equivalent to a χ^2 value of 172·514 with 165 degrees of freedom, which is an acceptable fit for the data as a whole.

Fig. 2 shows a contour map for values of $p(L_t)$ in the range 0·02 (0·0025) 0·20 and $p(L|DC)$ in the range 0·0 (0·025) 0·5, showing the differences between the optimal fit and the fit at other parameter values. The contours at different n-unit support differences (Edwards, 1972) give an idea of the acceptable range of the parameters. In particular, the value of $p(L|DC)$ of 0·2329 is not very different (0·202 units) from a value of 0·25, which would indicate an 'additive' inheritance (i.e. the heterozygote phenotypes). In view of the convenience of such a model (in particular since $p(C)$, the incidence of the C allele, may be shown to equal $2 \times p(L_t)$), the best fitting model will be taken as one in which $p(L|DC) = 0{\cdot}25$, these values providing numerical convenience. Model B is only 2·34 support units (likelihood ratio = 10·42) better fit than model A with the four outlying data points removed, and it may, therefore, be better for some purposes to use the parameter estimates from model A, since these include information from *all* studies rather than from those selected for being 'non-outliers'. For the rest of this paper I propose to consider a model (model C) in which $p(L_t) = 0{\cdot}0775$ and $p(L|DC) = 0{\cdot}25$. Elsewhere (McManus, 1979), I have considered (as a result of chi-square fitting rather than maximum likelihood fitting) a model in which $p(L_t) = 0{\cdot}095$ and $p(L|DC) = 0{\cdot}25$.

Table 6 shows, for model C, the expected proportions of left-handers in children from sibships of size 1–5, according to parental handedness, and Table 7 shows similar results for MZ and DZ twins. Tables 2, 3 and 5 show the expected values for model C, so that a comparison may be made between the observed and actual values.

It may be felt that by fitting the present model with corrections for $p(L_m)$ not equalling $p(L_t)$, I

Table 6. *The expected percentages for sibships of* 1–5 *of families with particular numbers of left-handed children* ($n(L)$) *by the handedness of the parents*†

	$n(L)\ldots 0$	1	2	3	4	5
Parents			One child			
R × R	94·025	5·975	—	—	—	—
R × L	82·575	17·425	—	—	—	—
L × L	71·125	28·875	—	—	—	—
			Two children			
R × R	89·056	9·937	1·007	—	—	—
R × L	68·716	27·718	3·566	—	—	—
R × L	50·997	40·256	8·747	—	—	—
			Three children			
R × R	84·897	12·479	2·426	0·198	—	—
R × L	57·569	33·441	8·137	0·854	—	—
L × L	36·819	42·535	17·849	2·797	—	—
			Four children			
R × R	81·393	14·014	3·937	0·610	0·046	—
R × L	48·513	36·223	12·547	2·484	0·233	—
L × L	26·739	40·316	24·596	7·401	0·947	—
			Five children			
R × R	78·427	14·831	5·374	1·188	0·168	0·012
R × L	41·090	37·115	16·329	4·584	0·813	0·070
L × L	19·517	36·110	28·571	12·422	3·040	0·339

† $p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

Table 7. *The expected proportions of twin pairs of type R–R, R–L and L–L by parental handedness and twin type*

	MZ twins			DZ twins		
Parents	R–R	R–L	L–L	R–R	R–L	L–L
R × R	89·722	8·606	1·672	89·056	9·937	1·007
R × L	70·369	24·412	5·219	68·716	27·718	3·566
L × L	53·638	34·975	11·388	50·997	40·256	8·747
NK	86·738	11·024	2·238	85·919	12·662	1·419

NK, not known.

have thereby gained an unfair advantage over the models of Rife and Trankell, since their models were fitted on the basis of different incidences of left-handedness reflecting different allele frequencies. I have therefore fitted the Rife and Trankell models to the entire data set (as used above in fitting model A) and also to the slightly reduced data set (as used in fitting model B with similar assumptions about $p(L_m)$ and $p(L_t)$). Table 8 shows the maximum likelihood estimates of the parameters, and the maximum support found. Since the models have identical numbers of parameters, their likelihoods may be directly compared in the form of the likelihood ratio (Edwards, 1972). It may readily be seen from Table 8 that the Rife and Trankell models are much less adequate fits of the data than the present model.

Table 8. *Comparison of maximum likelihood fits of the present model, and the models of Rife and Trankell when similar corrections are made for differences in manifest sinistrality*

	df	Maximum support	Difference from perfect fit	$p(L_t)$	2nd parameter†	Support difference from McManus
Fitted to total data			(χ^2, df = 169)			
Present model (model A)	2	−11446·441	231·410**	0·0767	0·2674	—
Rife	2	−11454·257	247·042***	0·0641	0·2177	7·816
Trankell	2	−11458·425	255·378***	0·0759	0·3813	11·984
'Perfect fit'	171	−11330·736	—	—	—	—
Fitted to reduced data set			(χ^2, df = 165)			
Present model (model B)	2	−9431·723	172·514	0·0642	0·2328	—
Rife	2	−9440·315	189·698	0·0417	0·1831	8·592
Trankell	2	−9438·845	186·758	0·0602	0·3703	7·122
'Perfect fit'	167	−9345·466	—	—	—	—

† 2nd parameter is $p(L|DC)$ for present model, $p(L|RL)$ for Rife model and $p(L|LL)$ for Trankell model.
**$P < 0·01$; ***$P < 0·001$.

Table 9. *Data from Leiber & Axelrod* (1981) *which were reported after the fitting of the model described in the text*

Parental handedness	Progeny handedness	
	R	L
R × R	1729 (1733·3)	173 (168·7)
R × L	281 (277·0)	63 (67·0)
L × L	8 (7·7)	3 (3·3)

$\chi^2_L = 0·462$, df = 1, NS.
$p(L_m)$ progeny = 0·1059; $p(L_m)$ parents = 0·0811; $p(L_t)$ = 0·0775; $p(L|DC) = 0·25$.
The values in parentheses are expected values.

15. AN *A PRIORI* TEST OF THE MODEL

After the above calculations had been completed the paper of Leiber & Axelrod (1981) was published, giving the proportions of families of type R × R, R × L and L × L in whom there was a left-handed child. These data thus represent a useful test of the model, since they were not used in estimating the parameters of the model. Furthermore, the sample size is large and the individuals are strictly independent, since only one child per parental pair has been included. Table 9 shows the data, and the predictions and fit for the expected values given model C, and estimates of $p(L_m)_{prog} = 0·1059$ and $p(L_m)_{par} = 0·0811$. It may be seen that these data are fitted very well by the model, and that this, therefore, represents a good test of the usefulness of the model.

16. A GENETIC MODEL OF HANDEDNESS: DISCUSSION

Thus far, I have described the fitting of a particular genetic model in which the true incidence of left-handedness in the population is 7·75%, the genotypes DD, DC and CC produce 0, 25 and 50% left-handers respectively, and for which differences in incidence of left-handedness between populations are accounted for entirely by response biases and criterion biases. This model will fit all the available twin data, all my own data from families of multiple sibships, and the majority of other parent–offspring studies in the literature. In particular, one large set of data was fitted adequately on an *a priori* rather than an *a posteriori* basis.

In fitting the models I have attempted, as far as possible, to fit all the available data. It is, of course, possible that published data sets are atypical, insofar as they may conform to particular types of model which fitted the received view of genetic control at that time, and that unpublished data remain in the 'file drawer' (Rosenthal, 1979). Two objections to this point can be raised: first, several of the modern studies reported are presented in an atheoretical context; secondly, if the objection were sustained it would become impossible to fit any genetic model to published data. The only remedy if the problem is a valid one is the collection and fitting of still more data.

A second problem in using all data sets is that

I have made the assumption that allele frequencies are the same in all populations, irrespective of their ethnic background. My reasons for this are two-fold: first, to do otherwise would have rendered the study impossible, since in most cases the ethnic mix of the populations is not clearly stated; secondly, to my knowledge there is no adequate evidence that the incidence of left-handedness differs between races, or between social classes within populations. In the first instance, therefore, a model may reasonably assume similarity between populations in allele frequency.

This model finds strong evidence for an additive rather than a dominant or a recessive mode of inheritance. This conclusion is similar to that found elsewhere for the inheritance of hand-clasping and arm-folding, both of which required models in which heterozygote manifestation was exactly intermediate between homozygotes, although three-allele models were required in that case (McManus & Mascie-Taylor, 1979). Three possible mechanisms for such an additive inheritance may be proposed:

(i) The additivity might depend purely upon the form of the dose–response relationship between the number of D alleles (0, 1, or 2) and the tendency of the gene-product to produce right-handedness.

(ii) The additivity of the alleles might be produced by the phenomenon of allelic restriction (Melnick & Shields, 1976), which is equivalent to autosomal lyonization. This could only be so if the gene produced its effect at an early enough stage in embryogenesis (i.e. that its action was expressed only in a single cell), but would produce a heterozygote expression mid-way between the two homozygotes.

(iii) The manifestation of the genes in the two sexes might be different. The classic example of this is the gene for *hornless* in sheep, which acts as a dominant in males and a recessive in females (Wood, 1905). The manifest incidence of left-handers is often higher in males than in females, and there is also a possibility of a tendency for children of left-handed mothers to show a great incidence of left-handedness than the children of left-handed fathers (Annett, 1973). (Whether such effects are differences in true handedness, or only in manifest handedness is not at all clear at present.) Since the effect of a male-dominant/female-recessive gene is formally equivalent to an additive model when the two sexes are combined, this possibility will not be considered further at the present.

The present model also allows an explanation of those rare cases in which a true biologically based pathological left-handedness is found, in which up to a 50% incidence of left-handedness may occur. A number of data sets have found an association between mental subnormality and left-handedness (see McManus, 1983*b*). These data sets have often been interpreted as evidence that left-handers in general are of lower intelligence, as if the handedness were somehow the cause of the mental deficiency. An alternative view is that a prior severe brain insult – e.g. due to trauma, metabolic or chromosomal abnormality – may have caused the low intelligence, and also have caused a great amount of 'biological noise' (see e.g. Siegel *et al.* 1977) which has over-ridden any pre-existing directional asymmetry to produce fluctuating asymmetry and hence left-handedness in up to 50% of cases. If true, then one might also predict that any other developmental abnormality of the brain might also produce a local increase in 'biological noise', and hence fluctuating asymmetry and 'phenocopy left-handers'. One possible example of this is in congenital partial or total agenesis of the corpus callosum. The condition is associated with normal intelligence, and is often detected only at routine post-mortem, or as an incidental finding on ventriculography or computerized tomography. Nevertheless, a review of the few cases in the literature for whom the handedness is given shows that, of the 19 cases, 9 (47·5%) were described as left-handed (Bossy, 1972; Dennis, 1976; Ettlinger *et al.* 1972; Ferris & Dorsen, 1975; Field *et al.* 1978; Gardner *et al.* 1975; Sadowsky & Reeves, 1975). Although this is a small sample, it is tempting to conclude that the incidence of left-handedness in callosal agenesis is indeed raised, as might be predicted from the theory.

17. A COMPARISON OF THE PRESENT MODEL WITH ANNETT'S MODEL

The most cited genetic model of handedness in the literature at present is that of Annett, which has been reviewed in several publications (Annett, 1978; Annett, 1981). The model has a number of interesting features, and a number of problems which make a direct comparison with the present model rather difficult, and hence the

comparison has been left to a late stage. A further comparison of the Annett model with the present one in the crucial case of the distribution of skill asymmetry will be found elsewhere (McManus, 1985).

Annett's model assumes that there are three genotypes, $--$, $-+$ and $++$, which are produced from two alleles $-$ and $+$, the $-$ and $+$ referring to right shift (RS) absent and right shift present. Annett assumes that, in the absence of a right shift, individuals of genotype $--$ will present a normal distribution of ability, with a mean of 0 and a standard deviation of 1 (the former is an important theoretical statement, the latter an arbitrary assumption). Thus, $--$ individuals are of population phenotype $N(0, 1)$ in which $N(m, s)$ indicates a normal distribution with mean m and standard deviation s. In the model she presented in 1978, Annett also proposed that heterozygotes, $-+$, acted as homozygotes, $++$ (i.e. the $-$ allele was recessive), and produced a population phenotype, $N(1{\cdot}937, 1)$, a shift of the distribution to the right being proposed. Annett suggested that handedness *per se* was dependent upon the position of an arbitrary criterion x and, as x shifted along the abscissa, so the proportion of left-handers in the population would change. The position of x is determined by equating the population manifest incidence of left-handedness with the sums of the areas under the left-hand tails of the two normal distributions up to the point x. Given an estimate of the allelic frequencies of $-$ and $+$ in a population (and these are assumed constant in all populations), one may calculate the proportion of $--$, $-+$ and $++$ in right-handers and left-handers; then, by the application of Mendelian genetics and knowing the threshold x in the progeny (which need not be the same as x in the parents), one may calculate the proportion of right- and left-handed children in the offspring of R × R, R × L and L × L matings. Annett has examined a number of data sets (Annett, 1978) and finds adequate fits. Annett actually derives her estimate of the gene-frequency, $p(-)$, from considerations of data on dysphasia. This does not seem to be a useful constraint, is quite possibly in error, and produces an unreasonable restriction in the models. I shall therefore derive my own estimate from purely internal considerations of the handedness data. Similarly, the degree of shift of $-+$ and $++$ genotypes is also derived by Annett (1978) from a consideration of dysphasic data. Again, this is likely to cause difficulty in fitting a model, and I shall derive my estimate entirely from internal considerations of the handedness data.

Annett found that a major problem in her fitting of the data was that twins did not produce sufficient numbers of discordant pairs. She therefore proposed that the $-+$ and $++$ twins came from a distribution $N(1, 1)$ – i.e. with a lesser right shift. Given this added assumption, her model also fitted twin data. The theoretical origin of this assumption is obscure, and it seems to receive primarily *a posteriori* justification in terms of the suspected differences between twins and singletons.

In the present analysis I shall use maximum likelihood methods to fit a number of variants of the Annett model to the total data set and to the reduced data set already described (and for which other estimates of fit have been given in Table 8). The models used vary along two dimensions. First, Annett's genetic model may be respecified since, while she originally assumed that the $-$ allele is recessive, she has recently sugested a model in which the heterozygote is intermediate between the homozygotes (i.e. a trimodal distribution) (Annett & Kilshaw, 1983). I shall thus fit three types of model:

A recessive (as in Annett, 1978);

B additive, in which the right shift of the $-+$ genotype is exactly half-way between that of $--$ and $++$ genotypes;

C intermediate, in which the right shift of the $-+$ genotype is anywhere between $--$ and $++$ genotypes (including, in extreme cases, recessive and dominant models).

The second dimension along which I shall allow the models to vary is whether singletons and twins have the same degree of right shift. It seems unlikely that they should have different degrees of shift, and thus the assumption should be rigorously tested. Models ending in a 1 assume no difference between singletons and twins, models ending in a 2 indicate that the shifts are allowed to be different. Thus model C2 allows heterozygotes to be at any intermediate position between the homozygotes, and singleton homozygotes to have a different right shift from twin

Table 10. *The results of fitting various forms of the Annett model of handedness to the total data and to the reduced data set*

	Support	Gene-frequency	Right shift in singletons: Homozygote	Right shift in singletons: Heterozygote	Right shift in twins: Homozygote	Right shift in twins: Heterozygote	Free-parameters	χ^2 difference from perfect	Support difference from McManus
Fitted to total data									
Annett model A1	−11473·756	0·4185	1·516	1·516	1·516	1·516	2	286·0***	27·315
Annett model A2	−11436·910	0·3656	1·999	1·999	0·883	0·883	3	212·3*	−9·531
Annett model B1	−11439·162	0·0422	2·975	1·487	2·975	1·487	2	216·9*	−7·279
Annett model B2	−11427·447	0·0781	2·726	1·363	1·527	0·763	3	193·4	−18·994
Annett model C1	−11439·079	0·0441	3·706	2·250	3·706	2·250	3	216·7*	−7·362
Annett model C2	−11427·404	0·0961	2·924	1·595	1·615	0·881	4	193·35*	−19·037
Fitted to reduced data set									
Annett model A1	−9457·849	0·2120	2·299	2·299	2·229	2·229	2	224·8**	26·126
Annett model A2	−9432·123	0·3138	2·017	2·017	0·967	0·967	3	173·3	0·400
Annett model B1	−9429·431	0·0207	3·468	1·734	3·468	1·734	2	167·9	−2·292
Annett model B2	−9424·151	0·0382	3·046	1·523	1·950	0·975	3	157·4	−7·572
Annett model C1	−9429·412	0·0199	3·880	2·122	3·880	2·122	3	167·9	−2·311
Annett model C2	−9425·488	0·1021	3·261	2·153	1·762	1·164	4	160·0	−6·235

*$P < 0·05$; **$P < 0·01$; ***$P < 0·001$.

homozygotes, although the position of the heterozygotes is assumed to be proportionately the same in singletons and twins.

Table 10 shows the maximum likelihood estimates of the parameters of the various models applied to the two sets of data. The table also shows the significance of the difference of the fit from a 'perfect' fit, and also the support difference between the Annett models and the model I have proposed earlier in this paper.

First, let us consider model A2, which is the one initially proposed by Annett. The maximum likelihood estimates of the parameters are similar to her estimates, except that the gene-frequencies are slightly lower. The model does not fit the total data adequately (although it is better than my model, albeit with one extra parameter), but it does fit the restricted data set adequately, and shows no significant difference from my own model. Considering just the reduced data set, the maximum likelihood estimates show an improved fit of 6·797 units over the estimates of Annett (1978) (equivalent to a relative likelihood of 895·2 times). If we allow the genetic structure of the model to change, by allowing either additivity or intermediacy of the heterozygote (models B2 and C2) it is clear that there is a significant improvement in fit, all of which is attributable to the additivity assumption, there being no further improvement with the assumption of intermediacy. In gaining this extra fit, however, the frequency of the − allele has dropped dramatically, and the right shift of the homozygous singletons has increased. Nevertheless, model B2 is an excellent fit to the restricted data set, as well as to the total data set.

Nevertheless, models A2, B2 and C2 have the assumption of different shifts in singletons and twins. If we remove this assumption then we find a different picture. Model A1 (recessive) is not an adequate fit to the total or restricted data sets, and is a much worse fit than my own model. Allowing additivity (model B1) greatly improves the situation. The model fits the restricted data set adequately, and is a slightly better fit than my own model. The introduction of intermediacy (model C1) produces no extra improvement in fit.

We must now consider the question of the Annett model versus my own. Each model has its pros and cons, and our decision as to which is 'best', on the basis of the present evidence, is a function of our acceptance or rejection of particular assumptions of each model. My own model assumes that there is, in some sense, a true incidence of handedness, and many would regard

this as unreasonable. It does, however, use a genetic model that makes biological sense, and relates to other well-known Mendelian systems. In contrast, Annett's model makes no assumptions about 'true' population incidences, but it does require the use of a relatively unusual genetic mechanism, coupled, in the case of models A2 and B2, with an unusual difference between singletons and twins. Furthermore, the two most adequate Annett models, B1 and B2, both require frequencies of the − allele much lower than she would probably find desirable, and which are unlikely to find any theoretical neuropsychological justification. If, however, one wishes to use Annett model A2 then there are no detectable differences, on present analysis, from the model which I proposed earlier.

However, it must be remembered that, as specified, the Annett models A2, B1 and B2, and my own model are different. They must, therefore, make different predictions about particular situations, and hence must, in principle at least, be discriminable. One specific prediction is that in my model it should, in principle, be possible to find pairs of individuals both of genotype DD who would 'breed true' for right-handedness; no such case is possible with Annett's model, since pairs of ++ individuals must, on occasion, produce left-handed offspring (for instance, if $p(\mathrm{L}) = 0{\cdot}08$, and the ++ genotype has a phenotypic distribution of $N(1{\cdot}937, 1)$, then 0·4% of the offspring of DD × DD matings will be left-handed).

Finally, it must be mentioned that the Annett model and my own can, if suitable parameters are chosen for each, become almost identical. Thus, if x, the criterion, is zero, then 50% of −− individuals will be left-handed. If the right shift of ++ individuals is a very large positive number then a vanishingly small proportion of them will be left-handed. If the right shift of heterozygotes, +−, is $N(0{\cdot}675, 1)$ then 25% of them will be left-handed. If the frequency of the − allele is now set at 0·155 then the model is an Annett-type model, but gives identical predictions to my own. In the ultimate analysis, therefore, the models cannot be discriminated on genetic grounds alone. The way out of this impasse is to consider the *phenotypic* structure of handedness that these models assume, and to fit that structure to data. This I have done elsewhere, and have argued that the right shift model of Annett fails (McManus, 1985).

A further factor to be considered is the utility of a model in making predictions beyond its immediate sphere of relevance. I would like to suggest that my own model can be extended to cover other forms of cerebral dominance, and propose to devote the rest of this paper to such predictions. It is not apparent how the Annett model(s) can accommodate such results, particularly given that, in the original model, the parameters were derived primarily from a consideration of such results but that a maximum likelihood analysis finds different and significantly better estimates of the same parameters.

18. A GENETIC MODEL OF LANGUAGE DOMINANCE AND APHASIA: INTRODUCTION

Thus far in this paper a model of the genetics of handedness has been proposed, and parameters have been estimated by considering only data based on studies of handedness. For the rest of this paper I shall extend the model to language dominance and aphasia, making detailed predictions about the incidence of aphasia in particular conditions, and fitting the model to the rather limited data that are available.

As with handedness, so with language dominance and aphasia there is a set of observations which any acceptable model must be able to explain:

(i) Cerebral speech dominance. This can be assessed in several different ways in normal subjects. The most common method, using dichotic listening, finds that about 15% of right-handers and 35% of left-handers show a left hemisphere effect (i.e. a right ear advantage). Results from unilateral ECT studies and from intra-carotid sodium amytal produce basically similar results.

(ii) Loss of speech after a unilateral cerebral lesion is more common if the lesion is on the left side of the head (about 40%) than if the lesion is on the right side of the head (3 or 4%).

(iii) In persons who have suffered loss of speech after a unilateral brain lesion, about 2–3% of right-handers and 20–30% of left-handers have a right-sided lesion. The incidence of crossed speech is thus estimated differently

from clinical cases, and from dichotic or ECT studies.

(iv) Left-handers seem both more prone to aphasia after a cerebral lesion, and also more likely to recover from such aphasia, so that overall the prognosis is better in left-handers than in right-handers (Gloning *et al.* 1969; Subirana, 1958, 1969; Goodglass & Geschwind, 1978; Hécaen & Albert, 1978; Hicks & Kinsbourne, 1978).

(v) A familial history of sinistrality seems to increase the probability of recovery from aphasia (Zangwill, 1960; Hicks & Kinsbourne, 1978).

19. THEORETICAL PREDICTIONS

Consider an individual of genotype DC. The model of handedness just proposed suggests that there is a 25% chance of that individual being left-handed, and a 75% chance of being right-handed. Suppose that there is also a 25% chance of that individual being right hemisphere dominant for language *and that that chance is independent of the chance of being left-handed.* Among DC individuals we would expect to find 1/16 who are left-handed and right language dominant, 9/16 who are right-handed and left language dominant, and the remaining 6/16 would show 'crossed laterality' (i.e. language dominance and hand dominance in opposite hemispheres). By a similar argument, one would expect that a quarter of CC individuals would be right-handed and left language dominant, a quarter would be left-handed and right language dominant, and a half would show crossed laterality. In contrast, all DD individuals would be right-handed and left language dominant. Given that 7·75% of the population is left-handed, and inheritance is additive, then one may predict that 5·98% of right-handers and 28·87% of left-handers would show right language dominance. By a similar argument, one may calculate the probability of an individual having right language dominance according to the individual's handedness, and that of his parents (Table 11). It is noteworthy from Table 11 that parental handedness has a relatively large effect upon the language dominance of right-handers, but only a minimal effect upon the language dominance of left-handers.

Table 11. *Expected incidence of right language dominance by handedness and parental handedness*

Parental handedness	Handedness (%) R	Handedness (%) L
R × R	4·55	27·99
R × L	14·78	29·96
L × L	24·59	39·44
NK × NK	5·98	28·88

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

Thus far, the model of language dominance might be used to predict the proportions of right-sided lesions among aphasics, according to handedness. However, the model would predict that 5·97% of right-handed aphasics would have right-sided lesions, a figure which is probably too high. We may, however, generalize the method and extend it, and thereby make better predictions concerning aphasia.

Once more, consider an individual of the DC genotype. Instead of considering just a single language dominance, consider two separate language dominances, which we may call language-A and language-B (LA and LB), each of which may manifest in the right or left hemisphere, the probability of having right-sided hand control or right-sided LA or right-sided LB being 25% *and the three probabilities being independent of one another.* We may now calculate the various probabilities of the R or L hemisphere controlling hand dominance or LA or LB.

Hand	Dominant hemisphere LA	Dominant hemisphere LB	Proportion
L	L	L	27/64
L	L	R	9/64
L	R	L	9/64
R	L	L	9/64
L	R	R	3/64
R	L	R	3/64
R	R	L	3/64
R	R	R	1/64

Similarly, for the CC genotype. For the DD genotype, all individuals will have left hemisphere dominance for hand control and for LA and LB.

As before, we may calculate the probabilities,

Table 12. *Expected pattern of language dominance (LL, B or RR) by handedness and parental handedness*

Parental handedness	Language dominance (%)...	Right-handers LL	Right-handers B	Right-handers RR	Left-handers LL	Left-handers B	Left-handers RR
R × R		92·09	6·67	1·24	52·52	38·99	8·49
R × L		74·65	21·13	4·22	50·06	39·98	9·96
L × L		59·90	31·02	9·08	38·20	44·72	17·08
NK × NK		89·70	8·64	1·66	51·41	39·44	9·16

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

by handedness of an individual, of having LA and LB in the left hemisphere (LL), LA and LB in the right hemisphere (RR), or of having LA in one hemisphere and LB in the other (bilateral language, B). Table 12 shows these predictions. Left-handers have a higher incidence of B and RR language than right-handers. Once again, parental handedness has a much greater effect upon the language dominance type of right-handers than left-handers. Even among the left-handed children of two left-handed parents there is a relatively low incidence of RR language (17·08%), and among the right-handed children of two right-handed parents a sizeable proportion have non-LL language (9·56%).

We may now consider what would happen in the event of a right- or left-sided brain lesion involving the appropriate areas of the hemispheres. A left-sided lesion in an LL individual would be expected to cause total and permanent loss of language, while in an RR individual there would be no evidence of aphasia. (It is assumed for the present that recovery from aphasia is not possible if both LA and LB are damaged, and that aphasia does not occur if LA and LB are not affected by the lesion.) The B individuals, who have LA in one hemisphere and LB in the other hemisphere, present a problem, for a left-sided lesion would remove one of the language centres but not the other. In such a case, I would propose that the acute effect of such a lesion is to produce an aphasia (or dysphasia), since the language centres have been damaged. However, the long-term result would be that recovery would occur, since not all of the speech centres have been removed. The model therefore discriminates between *acute* aphasia and *permanent* aphasia.

Table 13 shows the predicted proportion of

Table 13. *Expected incidence (%) of acute and permanent aphasia by handedness, parental handedness and lesion side*

Parental handedness	Right-handers Acute aphasia	Right-handers Permanent aphasia	Left-handers Acute aphasia	Left-handers Permanent aphasia
	Left-sided lesion			
R × R	98·76	92·09	91·51	52·52
R × L	95·78	74·65	90·04	50·06
L × L	90·92	59·90	82·92	38·20
NK × NK	98·34	89·70	90·84	51·40
	Right-sided lesion			
R × L	7·91	1·24	47·48	8·49
R × L	25·35	4·22	49·94	9·96
L × L	40·10	9·08	61·80	17·08
NK × NK	10·30	1·66	48·59	9·16

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

right- and left-handed individuals, according to parental handedness type, who would be expected to suffer an acute or permanent aphasia, according to the side of the lesion. Left-handers and right-handers with a family history of sinistrality are more likely to suffer aphasia after a right-sided lesion, and these same groups are less likely to suffer aphasia after a left-sided lesion. We may calculate from Table 13 the proportion of individuals with a particular type of aphasia who would be expected to have a right-sided lesion (Table 14). 1·81% of right-handers and 15·12% of left-handers with permanent aphasia would be expected to have a right-sided lesion. Once more, left-handedness and a family history of sinistrality make a right-sided lesion more likely in an aphasic, particularly in permanent aphasics. We may also

Table 14. *Expected percentages of acute and permanent aphasics who would have right-sided lesions by handedness and parental handedness*

Parental handedness	Right-handers		Left-handers	
	Acute aphasia	Permanent aphasia	Acute aphasia	Permanent aphasia
R × R	7·42	1·33	34·16	13·92
R × L	20·93	5·35	35·68	16·60
L × L	30·60	13·16	42·70	30·89
NK × NK	9·48	1·81	34·85	15·12

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

Table 15. *Expected percentages of individuals who have had an acute aphasia who will be expected to recover their speech by handedness, parental handedness and lesion side*

Parental handedness	Right-handers		Left-handers	
	Left-sided lesion	Right-sided lesion	Left-sided lesion	Right-sided lesion
R × R	6·75	84·32	42·61	82·12
R × L	22·06	83·36	44·40	80·05
L × L	34·12	77·36	53·93	72·36
NK × NK	8·78	83·91	43·41	81·16

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

calculate from Table 13 the expected proportion of acute aphasics who would be expected to recover from their aphasia (i.e. not progress to permanent aphasia) (Table 15). Left-handers are more likely than right-handers to recover from acute aphasia, and a family history of sinistrality makes recovery more likely, given that one has an acute aphasia.

Finally, we may consider the results of Table 13 combined by lesion side, assuming equal incidences of right- and left-sided lesions. Left-handers and those with a family history of sinistrality are more likely to suffer from acute aphasia, but, since they are also more likely to recover from such aphasia, are less likely overall to suffer from permanent aphasia.

From the account given so far, it will be clear that the LA–LB model of speech dominance and aphasia has potential, since it makes accurate predictions which appear to be related to the requirements specified earlier. It is therefore necessary to attempt to carry out detailed fitting of the predictions to actual data from studies, and this will occupy the next section.

It might be objected that, in invoking the LA–LB model, I have invalidated the earlier model which apparently gave reasonable estimates of the incidence of right-sided speech according to dichotic tests (Table 11). However,

Table 16. *Expected percentage of pairs of twins showing one twin with right language dominance (R–L) or both twins with left language dominance (L–L) and the expected ϕ coefficients of concordance for MZ and DZ twins by handedness of pairs (R–R, R–L or L–L) and parental handedness*

Parental handedness	Twin handedness	Language dominance...	MZ		DZ		ϕ_{MZ}	ϕ_{DZ}
			R–L	L–L	R–L	L–L		
R × R	R–R		5·15	0·92	7·11	0·56	0·2376	0·0991
	R–L		38·54	7·81	35·62	4·16	0·0241	−0·0345
	L–L		40·17	10·25	45·43	9·39	0·0497	−0·0421
R × L	R–R		17·98	3·41	24·57	2·40	0·1721	0·0202
	R–L		39·27	8·90	38·89	5·48	0·0372	−0·0393
	L–L		41·63	12·45	48·43	10·91	0·0623	−0·0627
L × L	R–R		26·96	7·08	41·39	6·17	0·1748	−0·0532
	R–L		43·46	15·19	53·99	10·39	0·0669	−0·1533
	L–L		46·65	19·98	58·88	16·20	0·0499	−0·1865
NK × NK	R–R		6·72	1·23	9·23	0·79	0·2336	0·0978
	R–L		38·86	8·29	36·75	4·69	0·0303	−0·0355
	L–L		40·86	11·28	47·00	10·19	0·0567	−0·0521
	NK–NK		11·02	2·24	13·25	1·42	0·2290	0·1044

$p(L_t) = 0{\cdot}0775$; $p(L|DC) = 0{\cdot}25$.

this is not the case. We need only to specify that one of LA or LB is more important than the other in determining dichotic listening asymmetry. Thus, if LA is the more important then an individual with LA in the left hemisphere would produce an (albeit relatively small) right-ear advantage. The predictions then follow Table 11 exactly as before.

Thus far, I have considered language dominance only in singletons. Considering only dichotic dominance (i.e. the simpler model) one may calculate the expected proportions of twin pairs who are concordant or discordant for side of language dominance (Table 16). From Table 16 it is clear that there is only a reasonable degree of concordance (as assessed by ϕ) among monozygotic R–R twins. Furthermore, among DZ twins there is actually a small degree of *discordance* predicted, although such a small degree would be difficult to demonstrate with statistical significance.

Predictions for twins on the LA–LB model will not be given, since they are more complex and are unlikely to be testable. However, they are straightforward, if tedious, to calculate.

20. TESTING OF PREDICTIONS IN NORMAL SUBJECTS

Having described the predictions of the genetic model in some detail, I shall now attempt to fit this model to a number of different data sets. From the start it must be made clear that, although we are dealing with a *genetic* model, there are no data sets which are strictly relevant to a genetic model, since in general chromosomal segregation has not taken place. This defect is, however, primarily a defect of data collection by research workers in general, rather than of the model in particular; in principle, such defects are easily remedied. Despite this limitation, the model still makes sufficient predictions to allow an examination of the relation between handedness and language dominance. If any serious mis-matches were to occur between such data and the model then the model would almost certainly be invalidated. In this section I wish to consider the relation between handedness and language dominance as assessed by three separate methods: dichotic listening tests, unilateral ECT, and intra-carotid sodium amytal.

Table 17 shows a summary of the results of 10 studies of the relation between handedness and language dominance as assessed by dichotic listening tests. These studies are variable. Some, but not all, use three separate categories for the classification of dominance (right, left and equal); in such cases I have amalgamated right and equal groups (the method of data fitting would also work if I had concatenated left and equal groups, although the arithmetic would be slightly different). Despite severe reservations, I have also added together results from different studies, because (*a*) some studies are too small to permit useful analysis on their own; and (*b*) most studies are not random population samples, but choose differing numbers of right- or left-handers, in some cases choosing only either right or

Table 17. *Cerebral language dominance as assessed by dichotic listening tests*

Study	Right-handers			Left-handers		
	L	R	No.	L	R	No.
Salz *et al.* (1967)	60	9	69	37	15	52
Curry (1967)	19	5	24	16	7	23
Zurif & Bryden (1969)	18	2	20	12	7	19
Dee (1971)	40	9	49	38	32	70
McGlone & Davidson (1973)	31	4	35	26	18	44
Blumstein *et al.* (1978)	27	11	38	—	—	0
Lake & Bryden (1976)	52	20	72	44	28	72
Davis & Wada (1977)	12	2	14	4	4	8
Lishman & McMeekan (1977)	19	3	22	13	7	20
Springer & Searleman (1978)	24	6	30	13	7	20
Total	302	71	373	203	125	328
Percentage right or equal		19·03			38·10	

Table 18. *Cerebral language dominance as assessed by unilateral ECT*

Study	Right-handers			Left-handers		
	L	R	No.	L	R	No.
Fleminger *et al.* (1970)	26	6	32	—	—	0
Pratt & Warrington (1972)	51	1	52	—	—	0
Warrington & Pratt (1973)	—	—	0	26	9	35
Annett *et al.* (1974)	17	2	19	2	2	4
Geffen *et al.* (1978)	22	2	24	6	3	9
Total	116	11	127	34	14	48
Percentage right or equal		8·66			29·16	

left-handers. Most studies have been careful to select subjects of fairly strong handedness, and therefore I have taken handedness assessments at face value; in any case it is impossible to make a direct estimate of the manifest population incidence of left-handedness in most studies. Overall, 19·03% of 373 right-handers were right hemisphere dominant (or showed no ear advantage at all); 38·10% of 328 left-handers were right hemisphere dominant (right *v.* left-handers: $\chi^2 = 31{\cdot}52$, df = 1, $P < 0{\cdot}01$).

In an interpretation of dichotic listening tests it is important to remember that the test–retest correlation is relatively low: Pizzamiglio *et al.* (1974) found that only 70% of adults showed the same dichotic category (right, left or equal) on two separate occasions; Blumstein *et al.* (1975) found a similar result, as did Bakker *et al.* (1978) in children. Account must be taken of this when fitting genetic models, since the incidence of apparent right language dominance will be artefactually raised (by a mechanism which is formally similar to that of Satz (1972): i.e. due to their numerical preponderance, true left hemisphere dominant individuals are more likely to be mis-classified as right dominant than vice versa, thereby raising the manifest incidence of right-hemisphere dominance).

Table 18 summarizes data from 5 studies of language dominance assessed by unilateral ECT. As with the dichotic studies, right hemisphere dominance and 'no hemisphere dominance' groups have been amalgamated, and handedness judgements have been taken at face value. In total, 8·66% of 127 right-handers had right-hemisphere dominance, while 29·16% of 48 left-handers had right-hemisphere dominance ($\chi^2 = 11{\cdot}96$, df = 1, $P < 0{\cdot}001$).

Table 19 summarizes data from two studies of language dominance assessed by intra-carotid sodium amytal. 9·09% of 143 right-handers and 42·85% of 161 left-landers had non-left hemisphere language ($\chi^2 = 43{\cdot}83$, df = 1, $P < 0{\cdot}001$).

Fig. 3 summarizes graphically the data from Tables 17, 18 and 19. The abscissa is the overall percentage of the condition in the population and thus varies according to the method used; it has been calculated by making the assumption that 7·75% of the population are actually left-handed, and then weighting the data of Tables 17, 18 and 19 appropriately. As with the studies of handedness, I therefore wish to propose that all these studies are actually measuring the same thing, and that differences between the studies are merely due to measurement error, differences in criterion, and so on.

It can be seen from Fig. 3 that the manifest incidence of right-sided language ($p(\mathrm{RL_m})$)

Table 19. *Cerebral language dominance as assessed by intra-carotid sodium amytal*

Study	Right-handers			Left-handers		
	L	R	No.	L	R	No.
Milner *et al.* (1964)	43	5	48	28	16	44
Milner (1975)	87	8	95	64	53	117
Total	130	13	143	92	69	161
Percentage right or equal		9·09			42·85	

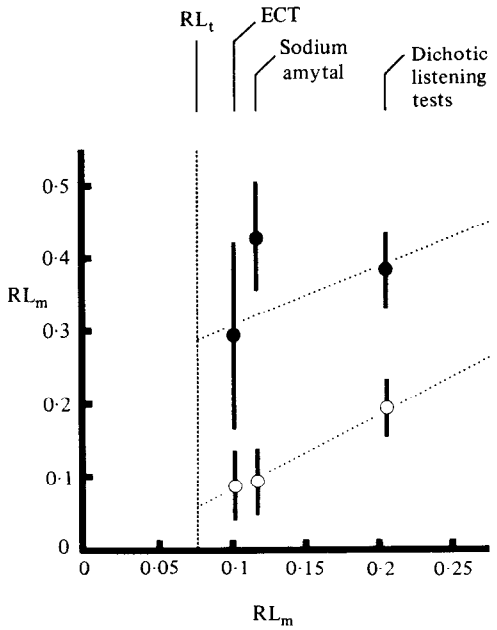

FIG. 3. The combined results of unilateral ECT, unilateral intra-carotid sodium amytal, and dichotic listening estimates of right-sided language dominance. The abscissa shows the overall manifest incidence of right language dominance, and the ordinate shows the manifest incidence of right language dominance in right-handers (○) and left-handers (●). Points are plotted along with their 95% confidence limits.

differs between studies. One may correct for such differences by means of a similar method to that described in the Appendix, assuming that if $p(RL_m)$ is greater than $p(RL_t)$ (the 'true' incidence of right-sided language as predicted by the model) then this is due entirely to some subjects with true left-sided language manifesting as right-sided language. Table 20 shows the observed and predicted values, and the significance of the difference between the observed and predicted values by means of the likelihood ratio criterion (χ^2_L). For dichotic studies and unilateral ECT the fit of the model is excellent. However, the fit of the sodium amytal data is much less good. This is possibly due to sampling problems, or to the unsuitability of the model for such a test, the LA–LB model perhaps being more appropriate. Nevertheless, the predictions are sufficiently good overall to justify continuing with the model.

Thus the model can cope with these data on handedness and cerebral language dominance. Although I am here fitting a *genetic* model to data, there are no actual data which a geneticist would find adequate, because there are no sufficiently large-scale, or well-defined, family studies of handedness and dichotic language dominance: the single exception of Bryden (1975) was not large enough to fit.

It is to be expected that, from the present type of model, there should be an increased incidence of right language dominance on dichotic tests if there is a family history of left-handedness. Table 11 shows the expected proportions of right language dominance in various family combinations. There are no adequate data in the literature to test these predictions exactly. Nevertheless, Zurif & Bryden (1969) have found increased proportions of right language dominance on dichotic tests in individuals with sinistral family histories, although the result is less than generally clear (for a review, see McKeever & Van Deventer, 1977). This lack of clarity is partly because of the inherent imprecision of the term 'familial sinistrality' (see Bishop, 1980) and partly due to the fact that the expected differences between R × R, R × L and L × L groups are fairly small, particularly for left-handed individuals, and are unlikely to be

Table 20. *The observed (predicted) numbers of right- and left-handers with right-sided language (RL_m) and left-sided language (LL_m) as assessed by dichotic listening tests, unilateral ECT and intra-carotid sodium amytal*

Source	$p(RL_m)$	Right-handers		Left-handers		χ^2_L	df
		RL_m	LL_m	RL_m	LL_m		
Dichotic listening tests	0·2051	71 (90·8)	302 (302·1)	125 (126·9)	203 (201·0)	0·053	1
Unilateral ECT	0·1025	11 (10·8)	116 (116·1)	14 (14·7)	34 (33·2)	0·063	1
Intra-carotid sodium amytal	0·1281	13 (15·9)	130 (127·0)	69 (52·7)	92 (108·2)	7·737**	1
Total						7·854*	3

* $P < 0·05$; **$P < 0·01$.

Table 21. *The observed (predicted) numbers of individuals with (A+) and without (A−) aphasia as a function of a right- or left-sided lesion*

Data set	χ^2_L (df = 1) Acute model	χ^2_L (df = 1) Permanent model	Model for expected values	Right lesion		Left lesion		$p(A_m)$
				A+	A−	A+	A−	
1. Conrad (1949)	4·743*	44·533***	Acute	18 (20·7)	249 (246·3)	185 (204·5)	172 (152·5)	0·2928
2. Hécaen & de Ajuriaguerra (1964)	2·535	27·567***	Acute	11 (11·8)	141 (140·3)	103 (114·1)	97 (85·9)	0·2937
3. Newcombe & Ratcliffe (1973) (acute cases)	2·759	60·431***	Acute	27 (27·8)	322 (321·2)	229 (245·7)	189 (172·3)	0·3126
4. Newcombe & Ratcliffe (1973) (permanent cases)	2·272	18·278***	Permanent	14 (4·2)	335 (364·7)	166 (186·4)	252 (231·6)	0·2175
5. Naumann (1955) (gliomata)	16·120***	1·248	Permanent	6 (3·8)	275 (277·2)	141 (137·5)	118 (121·5)	0·2829
6. Naumann (1955) (meningiomata)	1·993	3·076	Permanent	4 (1·5)	174 (176·5)	58 (61·4)	126 (122·6)	0·1688
7. Penfield & Roberts (1959)	37·127***	5·352*	Permanent	2 (3·6)	209 (207·4)	128 (114·9)	47 (60·1)	0·3705
8. Bingley (1958)	5·258*	1·843	Permanent	4 (1·9)	105 (107·1)	70 (70·8)	35 (34·2)	0·3517
9. Dennis & Whitaker (1977) (19th century)	55·045***	189·786***	—	43	207	127	214	0·2722
10. Dennis & Whitaker (1977) (20th century)	53·505***	164·985**	—	35	137	87	105	0·3283
Hécaen & Piercy (1956) (total)	76·276***	220·175***	—	45	146	81	142	0·2994
11. Hécaen & Piercy (1956) (expressive aphasia)	42·034***	130·209***	—	13	32	48	33	0·4407
12. Hécaen & Piercy (1956) (receptive aphasia)	1·493	6·930**	—	2	43	15	66	0·1148
13. Hécaen *et al.* (1981)	9·493**	60·308***	—	23	91	102	55	0·4257

* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

detected by small studies. Thus far, I have assumed that dichotic tests, unilateral ECT and intra-carotid amytal are actually assessing the *same* thing. This need not, however, be the case as far as the model is concerned, the only requirement being that the formal relationship with handedness be the same in each case (see also section 22 below). It is conceivable, for instance, that one test is assessing LA and another is assessing LB. Warrington & Pratt (1981) have presented empirical evidence that unilateral ECT and dichotic listening tests are not assessing the same asymmetric function.

Thus far, only language dominance in singletons has been considered. As shown in Table 16, the model makes clear predictions about language dominance in twins. However, the literature contains only a minimal amount of information about language dominance in twins (Springer & Searleman, 1978, 1980) and these data are too few to test the relatively small differences predicted in Table 16, although the results are at least compatible with those predictions.

21. TESTING OF PREDICTIONS IN BRAIN-DAMAGED SUBJECTS

The ideal data for fitting the LA–LB model would be from persons of known handedness and familial handedness with definite cerebral lesions on one side only, and for whom aphasia has been tested immediately after injury, and also some while after injury when recovery may have been expected to have taken place. In the absence of such a paragon, I shall attempt to fit the rather limited data at present available.

Table 21 lists 13 different sets of data. Conrad (1949), Hécaen & de Ajuriaguerra (1964) and Newcombe & Ratcliffe (1973; acute) examined the incidence of acute aphasia after cerebral lesions, Hécaen & Ajuriaguerra in patients with strokes, and the other two studies in patients with war wounds. Newcombe & Ratcliffe (1973; permanent) looked at the long-term follow-up of aphasia in their head injury patients. Naumann (1955) examined patients with either gliomata or

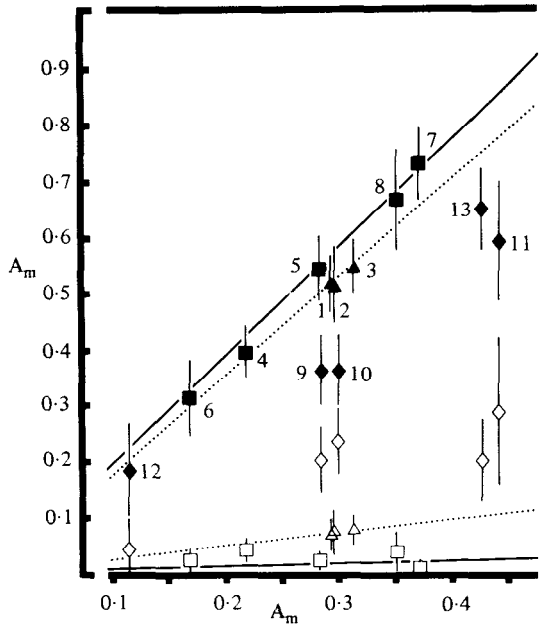

FIG. 4. The incidence of aphasia in 13 separate studies. The abscissa shows the manifest incidence of aphasia in the study as a whole, and the ordinate shows the incidence of aphasia in individuals with right (△, □, ◇) or left (▲, ■, ◆) hemisphere lesions. The 13 studies have been divided into three groups, according to whether the aphasia is acute (△, ▲), permanent (□, ■), or 'other' (◇, ◆); see text for further details. The numbers refer to Table 21. Points are plotted ± one standard error. The dotted lines indicate predicted values for the 'acute' model, and solid lines show the predicted values for the 'permanent' model, the upper lines indicating left lesions and the lower lines indicating right lesions.

meningiomata. Bingley (1958) examined patients with temporal lobe gliomata, coding as aphasic those who developed aphasia either before or after operation. Penfield & Roberts (1959) looked at acute aphasia after surgery in chronic epileptics. Dennis & Whitaker (1977) reviewed a large amount of data from studies examining long-term aphasia in children with severe cerebral injury or congenital spasticity, as a function of the side of the lesion; they looked separately at nineteenth- and twentieth-century data. Hécaen & Piercy (1956) examined the incidence of paroxysmal ictal aphasia in epileptic patients with unilateral foci, as a function of the side of the focus. Hécaen *et al.* (1981) examined the incidence of aphasia in patients with 'unilateral lesions, verified either surgically, clinically or paraclinically (X-rays, EEG and the CT scan)'.

Fig. 4 summarizes the data of Table 21. The abscissa is the overall incidence of aphasia in the study. It should be clear from this figure that the studies can be broadly grouped into three categories:

(i) The acute aphasias. The studies of Conrad, Hécaen & de Ajuriaguerra and of Newcombe & Ratcliff (temp).

(ii) The permanent aphasias. The studies of Bingley, Penfield & Roberts and Naumann seem to cluster above group (i) for left-sided lesions and below group (i) for right-sided lesions.

(iii) The studies of Dennis & Whitaker, Hécaen & Piercy, and Hécaen *et al.* are clearly distinct from either group (i) or (ii). These studies are probably not suitable for the present form of analysis, since there is little certainty that the lesions are truly unilateral, in each case it being possible that bilateral damage has occurred (and hence the greater similarity of 'right'- and 'left'-sided lesions).

In fitting the model to these data sets I have assumed, as earlier, that $p(L_t) = 0{\cdot}0775$ and $p(L|DC) = 0{\cdot}25$. As stated earlier, the model makes two separate predictions according to whether the aphasia is acute or permanent. For a particular data set it is not always clear which variant of the model should be fitted, and I have therefore always fitted both variants of the model to all data sets. This is necessary, since (*a*) if both variants fit for all data sets then the differentiation between the forms is clearly trivial; and (*b*) for some studies, particularly those involving chronic epileptics, it is not at all clear which is the appropriate form of the model (see below).

In fitting these data sets several assumptions have had to be made. First, the genetic model predicts the various proportions of the language dominance phenotypes and then the expected incidences of acute and permanent aphasia after right- and left-handed lesions. However, corrections must be made for the incidence of right-sided lesions not equalling the incidence of left-sided lesions (see Table 21 for the actual proportions). More controversial is the correction for the overall incidence of aphasia. Let the overall manifest incidence of aphasia in a study be A_m. There is also an expected 'true' incidence of aphasia from the genetic model (i.e. equivalent to Table 13) which we may call A_t. A_m may not equal A_t for many reasons. Consider a study of aphasia after head injury; if one examined only patients who had required neurosurgical intervention then the incidence of aphasia would be high (and, indeed, may even be overly high, for aphasia may itself have been a criterion for

operation). Alternatively, if one had studied all patients with head injuries, however minor, but who had had, say, loss of consciousness and been brought into a casualty department, then the overall incidence of aphasia would be far lower. In the latter example we may postulate a simple dilution effect, whereby if in any sub-group the expected proportion of aphasics was p, and A_m/A_t equalled 0·001, then the corrected value for the sub-group would be $0{\cdot}001p$. The severity of lesion is not the only factor which would affect A_m: it will also be affected by the location of a cerebral lesion. Thus if a large proportion of lesions is occipital, or cerebellar, we would expect a lower incidence of aphasia than if all lesions were fronto-temporal. A further complication for the model fitting is that, as with handedness and dichotic studies, different criteria may be adopted for aphasia. Some studies may, perhaps inadvertently, have included more expressive than receptive aphasics (due to the greater ease of detection); or studies might have had a sensitive threshold for dysphasia so that the slightest hesitation, stammer or mis-pronunciation might count as aphasia for the purposes of the study. All such factors will mean that A_m will vary between studies. I have used the single correction described above to account for all such effects, partly because of its simplicity, and partly due to the lack of any adequate, more detailed information on which to base more complex corrections. The single correction cannot hope to correct perfectly for all of the deviations of A_m from A_t. If too strict a criterion of aphasia is employed it should be true that all cases reported as aphasia really will be aphasia. If the criterion is too slack then an increasing proportion of non-aphasics will be included in the aphasic group. But these non-aphasics will have, on average, 50% of right-sided lesions, and thus the ratio of right- to left-sided lesions will be distorted. No such distortion will take place for too strict a criterion (this might, in principle, provide an empirical approach to the question of what is 'really' the correct definition of an aphasic).

It might be objected that I have used so many corrections in fitting the models to the data that it would be possible to fit almost any data set which I cared to try. There are two arguments against this.

(i) Later it will be shown that there are clearly some models which do *not* fit, and hence we may assume that we have at least one remaining degree of freedom in our goodness-of-fit testing.

(ii) In Table 21 I have included several data sets, those of Dennis & Whitaker and Hécaen & Piercy, which cannot act as a reasonable test of the present model (since they clearly do not exclude possible bilateral lesions), and thus these data should *not* be fitted by the present models: and this will subsequently be shown to be the case.

For acute aphasia A_t in Table 21 is 0·5551, and for permanent aphasia it is 0·4449. In general, A_m is less than these values. The data sets of Conrad (1949), Hécaen & de Ajuriaguerra (1964) and the acute cases of Newcombe & Ratcliffe (1973) clearly require the fitting of the acute model, and Table 21 shows that, in general, the acute model provides an adequate fit, whereas that of the permanent model is unsatisfactory. The data sets of Naumann (1955), Penfield & Roberts (1959) and Bingley (1958) and the permanent aphasia data of Newcombe & Ratcliffe all require the permanent model of aphasia and, with the exception of Newcombe & Ratcliffe, are fitted adequately by the permanent model, although in some cases the acute model also fits. Why these data sets require the permanent model, and the failure of the model to fit the Newcombe & Ratcliffe data, will be discussed later. The data of Dennis & Whitaker (1977), Hécaen & Piercy (1956) and Hécaen *et al.* (1981) are not fitted by either the acute or the permanent model. As suggested earlier, this is probably due to the inclusion of bilateral lesions in unknown proportions and thus, in a sense, represents a negative test of the model. If it is felt that this explanation is unreasonably *ad hoc* then the alternative is that we must provide some other explanation for the heterogeneity of the results shown in Fig. 4.

Thus far, the model fitting has paid no account to the handedness of individuals. There are rather fewer adequate data sets with information on handedness. Table 22 summarizes 6 such data sets. In fitting the model to these data sets the assessments of handedness have been taken at face value. From the observed incidence of left- and right-sided lesions, and right- and left-handedness, a corrected estimate of $p(A_m)$ has been calculated, on the assumption that right- and left-sided lesions are truly equally common, and $p(L_t) = 0{\cdot}0775$. The predicted incidences within side/handedness sub-groups (Table 13)

Table 22. *The goodness-of-fit of the acute and permanent models of aphasia to 6 sets of data*

Data set	χ^2_L (df = 3)		Model for expected values	Right-handers				Left-handers				$p(L_m)$	$p(A_m)$
				Left lesion		Right lesion		Left lesion		Right lesion			
	Acute model	Permanent model		A+	A−	A+	A−	A+	A−	A+	A−		
Conrad (1949)	2·212	41·76***	Acute	175 (176·4)	163 (161·6)	11 (13·6)	238 (235·4)	10 (9·2)	9 (9·8)	7 (4·6)	11 (13·4)	0·0592	0·2946
Hécaen & de Ajuriaguerra (1964)	35·052***	67·004***	Acute	81 (80·9)	82 (82·1)	0 (6·8)	130 (123·2)	22 (12·4)	5 (14·6)	11 (5·4)	11 (16·6)	0·1392	0·2802
Newcombe & Ratcliffe (1973) (acute)	0·297	55·392***	Acute	218 (218·3)	170 (169·7)	19 (18·6)	297 (297·4)	11 (10·4)	9 (9·6)	8 (9·2)	25 (23·8)	0·0691	0·3175
Newcombe & Ratcliffe (1973) (permanent)	3·499	17·012***	Permanent	158 (169·9)	230 (218·1)	9 (2·6)	307 (313·4)	8 (7·5)	22 (22·5)	5 (1·5)	28 (31·5)	0·0691	0·2171
Penfield & Roberts (1959)	31·673	8·006*	Permanent	115 (117·4)	42 (39·6)	1 (2·7)	195 (193·3)	13 (7·7)	5 (10·3)	1 (1·1)	14 (13·9)	0·0855	0·3707
Bingley (1958)	8·950*	5·186	Permanent	68 (70·5)	33 (30·5)	1 (1·3)	98 (97·7)	2 (1·6)	2 (2·4)	3 (0·7)	7 (9·3)	0·0654	0·3462
Hécaen *et al.* (1981)	22·956***	105·484***	Acute	36 (39·4)	34 (30·6)	5 (3·5)	55 (56·5)	66 (45·3)	21 (41·7)	18 (15·0)	36 (39·0)	—	0·3180

The values in parentheses represent the expected proportions based on the model described in the fourth column.
* $P < 0·05$; ** $P < 0·01$; *** $P < 0·001$.

were corrected by a factor $p(A_m)/p(A_t)$. Goodness-of-fit testing is by the likelihood ratio criterion. As with Table 21, the acute and permanent models have each been fitted to each of the data sets.

The results of Conrad (1949) are fitted well by the acute model, and the permanent model does not fit these data well at all. The data of Hécaen & de Ajuriaguerra (1964) are not fitted by either the acute or the permanent model. This is surprising, since the model ignoring handedness (Table 21) fitted the data well. Annett (1975) has suggested that the data of Hécaen & de Ajuriaguerra (1964) are not satisfactory, since there is evidence that handedness was not classified independently of language dominance. This is suggested in the present analysis by the fact that the major discrepancy is in right-handers with right-handed lesions, *none* of whom have aphasia, as compared with a predicted 6·8 cases. This discrepancy is striking in comparison with the other data sets, and makes one suspect that some such individuals have been classified as left-handers. Such an interpretation is supported by the fact that this study has a far higher $p(L_m)$ than the other studies (and, indeed, the other studies are remarkably close to the predicted $p(L_t)$ of 0·0775). The Hécaen & de Ajuriaguerra data cannot therefore be regarded as an adequate test of the model. The acute aphasia data of Newcombe & Ratcliffe (1973) provide an excellent fit to the predictions of the model. The permanent aphasia data, as reported by Newcombe & Ratcliffe (1973), do not provide an adequate fit to the data. However, Newcombe (1979), at a meeting of the International Neuropsychological Society in Dubrovnik, is reported to have said that the number of permanently aphasic right-handed right-lesioned men should probably be reduced to either one or none. Without further information it is difficult to assess this claim adequately. However, if one assumes that only one of this group of 316 individuals was permanently aphasic then the permanent model gives a χ^2_L of 7·274 (df = 3, NS), as compared with a similar χ^2_L of 21·44 for the acute model. Clearly, such a re-evaluation of the data is of crucial importance for the present model.

The data sets of Penfield & Roberts (1959) and Bingley (1958) are both fitted reasonably by the permanent model: the question of why the permanent model is more appropriate for these data is deferred until a later section.

As might be expected from the earlier reservations about the data of Hécaen, a reasonable fit cannot be found for the data of Hécaen *et al.* (1981) in which handedness is taken into account. An examination of the expected values in Table 22 shows that the poor fit of the acute model is entirely due to an excess of aphasia among left-handers with left-sided lesions: there is no clear explanation for this finding.

22. VISUO-SPATIAL DOMINANCE, LANGUAGE DOMINANCE AND HANDEDNESS

Thus far, the model has concentrated on handedness and language dominance. The possibility has been raised that some individuals have LA on one side and LB on the other side due to the statistically independent effects of fluctuating asymmetry. Once this possibility has been allowed then we may extend the principle to other forms of dominance. It is commonly thought that, in the majority of individuals, the right hemisphere is dominant for visuo-spatial processing (VSP). If a proportion of individuals have left hemisphere VSP, and the determination of the laterality of VSP is by a similar mechanism to that of LA and LB, then we may predict that some individuals will have, say, LA in the left hemisphere, LB in the right hemisphere, and VSP in the left hemisphere etc., a total of eight separate combinations being possible. All types except for LA and LB in the left and VSP in the right hemisphere should be more common in left-handers than in right-handers.

By means of similar calculations to those performed earlier, the model provides clear predictions as to the proportions of the various phenotypes. Language dominance and visuo-spatial dominance were assessed separately (by dichotic and tachistoscopic tests respectively). The manifest incidence of right language dominance (assuming that handedness is assessed correctly, and $p(L_t) = 0{\cdot}0775$) is 0·3047. The manifest incidence of left VSP is 0·1245. The predictions from the model (which are essentially obtained by using the results of Table 12 and substituting VSP for LB) must be corrected for the manifest incidences of right language

Table 23. *Language dominance, visuo-spatial dominance and handedness*

Language dominance	L	L	R	R
Visuo-spatial dominance	R	L	R	L
Right-handers	19	2	5	1
	(19·2)	(1·4)	(7·5)	(1·9)
Left-handers	15	8	5	8
	(13·2)	(6·1)	(11·1)	(5·6)

$\chi^2_L = 6{\cdot}646$, df = 3, NS.
Data from McGlone & Davidson (1973) as quoted by Levy (1976).
The values in parentheses are expected values.

dominance and left VSP dominance, and are shown in Table 23. The likelihood criterion test for goodness-of-fit gives a value of 6·646 (df = 3, NS). Hence we may regard the predictions of the model as also being of use for visuo-spatial dominance in relation to handedness and language dominance.

23. A GENETIC MODEL OF LANGUAGE DOMINANCE AND APHASIA: DISCUSSION

In section 19 I have presented a formal model of handedness, and language dominance and aphasia, and in sections 20, 21 and 22 I have tested the detailed predictions of such a model on the limited empirical data available in the literature; the results, in general, were reasonably compatible with the model.

The language-A, language-B, as proposed, is purely *formal*; there is no suggestion or implication that these two speech centres are related to Broca's or Wernicke's areas – indeed, from the point of view of the present approach both those systems could themselves have several independent random asymmetric phenotypes. It is worth noting in this context that Cutting (1974) has suggested that there are at least two independent mechanisms involved in the dominance of the left hemisphere for speech perception. Eight phenotypes are proposed, from handedness (H), LA and LB all being in the left hemisphere to H, LA, and LB all being in the right hemisphere. Naturally, some of these phenotypes will be far more common than others, with LLL (i.e. H, LA and LB in that order) being most common, and RRR being the rarest.

In order to make such a model compatible with the earlier, intermediate model of dichotic listening data one merely has to say that LA has more effect on dichotic tasks than LB. If LA and LB are both in the left hemisphere we would expect a strong right-ear advantage (REA), while if LA and LB are both in the right hemisphere we would expect a strong left-ear advantage (LEA). But if LA is in the left hemisphere and LB is in the right hemisphere we would expect only a modest REA, and if LA is in the right hemisphere and LB is in the left hemisphere we would expect only a modest LEA. Equating weak and strong ear advantages, the LA and LB model of dichotic listening becomes isomorphous with that described at the beginning of section 19 and in Table 4, and fitted to the data in section 20.

The LA–LB model has several important consequences for dichotic listening tests. There has been much controversy over the optimal way in which to describe an individual's dichotic asymmetry score; thus some authors use the simple score (L − R), while others use (L − R)/(L + R), or other variants upon the basic data; Colbourn (1978) has even suggested that it is possibly not valid to measure the degree of dominance. Either way, I would suggest that the present controversy is partially misguided in the absence of some understanding (or even simple description) of the underlying structure of the scores. Graphs of the distribution of dichotic asymmetry scores are rare; in general, only means and standard deviations are given. There are, however, anecdotal reports to the effect that REAs seem more robust than LEAs; and that those individuals with REAs seem to divide into two gross categories: those with strong ear advantages and those with weak ear advantages (see Berlin & Cullen, 1977; Hicks & Kinsbourne, 1978).

Drawing upon a combination of such anecdotes and upon my proposed genetic model, I would therefore suggest that dichotic asymmetries may have a structure of the form shown in Fig. 5. There is a quadrimodal distribution, heavily skewed to a right-ear advantage. The height of peaks *B* and *C* will be identical. In individuals with a right-ear advantage, the absolute size of the ear effect ought to be greater than in those with a left-ear advantage (since $D > C$ and $B > A$). If the noise distributions (due to either real individual differences or to measurement errors) around *A*, *B*, *C* and *D* are larger then (*a*)

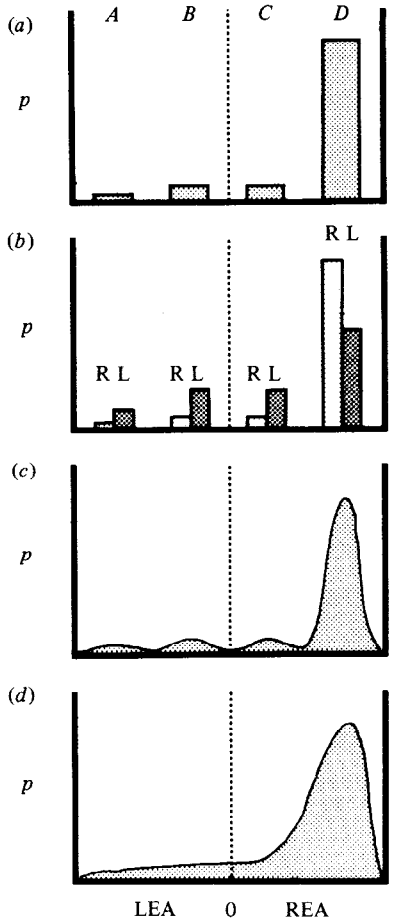

FIG. 5. Some hypothetical distributions of laterality coefficients. The ordinate represents probability density, and the abscissa is measured in units of ear advantage (REA, right-ear advantage; 0, no ear advantage; LEA, left-ear advantage). (*a*) The relative proportions of the four hypothesized laterality types (*A* corresponding to language type RR, *B* and *C* to types RL and LR; and *D* to type LL); (*b*) the same distributions, but separately for right (R) and left (L) handers; (*c*) the distribution of (*a*), but with the addition of a moderate amount of error of measurement; (*d*) the distribution of (*a*) but with a large amount of error of measurement.

there will be a poor test–retest correlation for those in categories *B* and *C*; and (*b*) the overall distribution will superficially resemble a skewed unimodal normal distribution. Such a model will explain several of the problems associated with dichotic listening tests; it perhaps also shows the potential folly of merely calculating the mean scores of individuals when underlying distributions have not been shown to be normal.

The model of Fig. 5 would also predict that left-handers would have a lower mean asymmetry score and a greater variance of asymmetry score than right-handers. This result does not require a quadrimodal distribution (see McManus, 1983*a*); however, the presence of a quadrimodal distribution would produce such a result within a group with either a right-ear advantage or a left-ear advantage, as well as in the whole population.

In fitting the LA–LB model to the effects of cerebral lesions in causing aphasia, I have made a number of formal assumptions for the purpose of simplicity. None of these assumptions need be correct, and a family of more complex models could be created in which such assumptions were modified.

(i) It is assumed that if LA and LB are both in the same hemisphere, and that hemisphere suffers a lesion, then *either* both LA and LB will be damaged, resulting in aphasia, *or* neither LA nor LB will be damaged, resulting in no aphasia. This assumes that LA and LB are topographically identical, which is perhaps an unreasonable assumption. If it is possible to damage LA and not LB, or vice versa, then the predictions of the model are different, depending upon the degree of overlap (or correlation) of the two 'areas' (speaking semi-metaphorically).

(ii) It is assumed that all lesions are neither progressive nor reversible: that is, their effects are immediate and without change. Of course, diseases or injuries of the brain do not work in this manner; in particular, any acute lesion causes cerebral oedema which is frequently reversible, often resulting in a decrease in the actual functional lesion size. Some lesions are progressive – neoplasms would be the obvious example – but cerebral thrombosis can produce oedema, which may produce further thrombosis in already compromised arteries. Account could perhaps be taken of these factors in a model – e.g. an index of decreased lesion extent.

(iii) It is assumed that the lateral expressions of H (handedness), LA and LB in the DC and CC genotypes are statistically independent. A set of models could be constructed in which the events were not completely independent, but instead showed some correlation with one another; these correlations need not even be identical, so that, say, that between LA and LB may be greater than that between H and LA.

(iv) It is assumed, for all three genotypes, that the expression is identical for H, LA and LB.

Thus if in the DC genotype there is a probability of left-handedness of 0·25, there is also assumed to be a probability of 0·25 of right LA, and 0·25 of right LB. Of course, there is no reason why these probabilities should be identical, and it is conceivable, for instance, that DC might produce 0·25 left-handers, 0·35 right LA, and 0·45 right LB.

Perhaps the most interesting consequence of the model is its differentiation of acute and permanent aphasia, by means of considering whether, in the acute phase, *either* LA *or* LB has been damaged and, in the later phase, considering whether *both* LA *and* LB have been damaged. It is this feature of the model which allows us to reconcile the relatively high incidence (9·5%) of apparent right language dominance in right-handers, from the assessment of acute aphasia, with the much lower incidence (1·8%) of apparent right language dominance in the typical right-handed 'crossed aphasic' who is eventually seen in a clinic by a neuropsychologist and almost certainly has a permanent aphasia (Table 14).

One may speculate on the mechanism of this difference between acute and permanent aphasia. In an ordinary individual with LA and LB in different hemispheres, there is presumably a high degree of interaction between the two centres. If one centre is suddenly destroyed then we may assume that this will, acutely, disrupt the functioning of the intact hemisphere, and that aphasia will result. However, given time, such patients may be expected to recover the function of the remaining intact centre. Such a process has been previously proposed by Riese (1970), who invokes von Monakow's (1914) concept of *diaschisis commissuralis*:

> Speech defects of right-handed individuals may result from lesions of the *right* hemisphere throwing out of function the left hemisphere as the result of cerebral shock, or diaschisis; but as a rule, these effects of cerebral shock, are transient. Thus the question of cerebral localisation has to be answered in a different way, according to the two major stages of brain injuries and brain disease, those of initial or transient, and those of residual or lasting symptoms.

The mechanism of the interaction may perhaps be less psychological (i.e. functioning is impaired) and more physiological, the whole process perhaps being akin to spinal shock. Immediately after spinal section there is a complete loss of spinal reflexes below the lesion as a result of a loss of descending tone. After a variable period, however, this shock disappears and, indeed, the reflexes become hyperactive. Of more interest in this analogy is that if a second section is made below the first then no spinal shock is seen. From this we may speculate on the role of the repeated insult to one or other of the speech centres. The most relevant example of this would be found in chronic epileptics, who make up much of the population of persons whose speech is examined by amytal, split-brain techniques etc. (although other reversible lesions would also be relevant, such as aphasia as a result of transient ischaemic attacks). I would like to propose that, in such cases, the continual insults render LA and LB autonomous, so that after an irreversible *acute* lesion the individual would become aphasic only if he would in any case have become *permanently* aphasic as a result of such a lesion. By such a hypothesis we may account for the fact that for the studies of Penfield & Roberts (1959) and Bingley (1958) the data are better fitted by the permanent model than by the acute model. Similarly, for lesions with a slow insidious development, such as the meningiomata and gliomata data of Naumann (1955), the permanent model will provide a better fit than the acute model, since diaschisis will not develop.

A further implication of the model is of some therapeutic and medical consequence. In Table 15 I have given exact predictions for the probability of recovery from aphasia. I have not, in that table, made any allowance for the effects of treatment (merely assuming that the underlying pathology is irreversible, and ignoring potential effects due to the regression of intra-cerebral oedema, etc.); in particular, the model predicts that speech therapy will, indeed *can*, have no consequence on the overall rate of recovery from aphasia. It may affect the speed of recovery, but it should not affect the overall incidence of recovery. This conclusion is compatible with several reviews of the effects of speech therapy (Sarno *et al.* 1970; Darley, 1975; *Lancet*, 1975; Levita, 1978) which find no demonstrable effect of therapy on the incidence of recovery. Similarly, several studies have found no difference between professional speech therapists and amateur or volunteer speech therapists (Lesser & Watt, 1978; Meikle *et al.* 1979). A controlled trial of speech therapy in aphasia (Basso *et al.* 1975)

found that speech therapy improved recovery if therapy was started within two months of a lesion, and that it had no effect six months after a lesion had occurred; that study cannot, however, differentiate between an increase in the speed of recovery of those who would have recovered in any event and an actual increase in the overall incidence of recovery of speech. The uncontrolled study of Gloning *et al.* (1976) found a positive effect of speech therapy; the uncontrolled study of Lincoln *et al.* (1982) and their controlled study (Lincoln & Pickersgill, 1984; Lincoln *et al.* 1984) found no such effect.

The present model also has implications for work involving possible language functions in the right hemisphere. Among right-handers, 10·3% may be expected to have *some* language function in the right hemisphere. Consequently, the interpretation of individual cases of apparent language in the right hemisphere of right-handers – for example, after hemispherectomy or callosal section – becomes very complex. The model would also predict that a proportion of individuals, particularly chronic epileptics or those suffering repeated ischaemia, will apparently have bilateral language centres on a sodium amytal test.

In considering the relation of language dominance to visuo-spatial processing dominance I suggest that each of these may be a result of independently determined fluctuating asymmetry. Once one has opened the Pandora's box of multiple, independent random phenotypes contingent upon the same genotype, then many possibilities arise for theoretical explanation and speculation. If we allow the possibility that the two language centres *and* a 'visuo-spatial' centre are each determined independently, then it is readily apparent that there may well be individuals with, say, LA on the left, LB on the right and also visuo-spatial analysis on the left; and so on. Naturally, the more bizarre arrangements (i.e. all phenotypes except the archetypal pattern of LA, LB and hand control on the left, and visuo-spatial on the right) will be more common in left-handers. We now only have to speculate that it is functionally or anatomically inconvenient to have, say, language in opposite hemispheres, or language and visuo-spatial analysis in the same hemisphere, to provide theoretical explanations of such data as find an excess of left-handers in groups such as stutterers or dyslexics, or that such individuals tend to have less asymmetry on dichotic or tachistoscopic tests. We may perhaps also explain the increased incidence of left-handers and the thicker than usual corpus callosum in schizophrenics (Lishman & McMeekan, 1976; Gur, 1977; Rosenthal & Bigelow, 1972; Bigelow *et al.* 1983), and some of the more bizarre neuropsychological conditions might fall within the scope of the model once we propose that, say, a lateralized reading centre and a lateralized writing centre are both independent random phenotypes. Cases of aphasia and alexia without agraphia, would now be possible, albeit rare, with a single lesion. The possibility that all possible lateral combinations of language, handedness and visuo-spatial analysis might occur has already been proposed by Kreindler *et al.* (1966). The concept of multiple independent dominance functions has been proposed in passing by Goodglass & Kaplan (1963), and more explicitly by Hardyck (1977); the present paper allows more precise predictions to be made about such models.

APPENDIX: THE CALCULATIONS

In general, the calculations are standard genetic manipulations involving matrix multiplication of various forms (see Smith, 1976, for an excellent introductory account). The major innovation in the present study is the method of taking account of differences in incidence of manifest handedness between studies, and between generations within a study.

Let the true incidence of left-handedness be t, and the particular incidence be p for the progeny and q for the parents. Given a particular value of t, and assuming that the Mendelian system has been specified (i.e. the values of $p(\mathrm{L}|\mathrm{DD})$, $p(\mathrm{L}|\mathrm{DC})$ and $p(\mathrm{L}|\mathrm{CC})$) then we may calculate a 3×2 matrix $\mathbf{T}$, which contains the probability of a child of particular true phenotype, given the particular true phenotypes of the parents (where $\mathrm{R_t}$ and $\mathrm{L_t}$ represent particular true phenotypes, and $\mathrm{H_t}$ represents either true phenotype):

$$\mathbf{T} = \begin{bmatrix} p(\mathrm{R_t}|\mathrm{R_t} \times \mathrm{R_t}) & p(\mathrm{L_t}|\mathrm{R_t} \times \mathrm{R_t}) \\ p(\mathrm{R_t}|\mathrm{R_t} \times \mathrm{L_t}) & p(\mathrm{L_t}|\mathrm{R_t} \times \mathrm{L_t}) \\ p(\mathrm{R_t}|\mathrm{L_t} \times \mathrm{L_t}) & p(\mathrm{L_t}|\mathrm{L_t} \times \mathrm{L_t}) \end{bmatrix}.$$

The problem is to correct $\mathbf{T}$ into a matrix $\mathbf{M}$ for which the elements are $p(\mathrm{H_m}|\mathrm{H_m} \times \mathrm{H_m})$, the subscript m indicating manifest handedness.

Consider first the progeny. Let $p > t$. We therefore assume that, since the manifest incidence of left-handedness is higher than the true incidence, this is entirely a result of some true right-handers manifesting as left-handers. We may thus construct a 2×2 transition matri **P** the elements of which are $p(H_m|H_t)$:

$$\mathbf{P} = \begin{bmatrix} p(R_m|R_t) & p(L_m|R_t) \\ p(R_m|L_t) & p(L_m|L_t) \end{bmatrix}.$$

Since $p(R_m|L_t) = 0$, the rest of the matrix is defined as:

$$\mathbf{P} = \begin{bmatrix} 1-u & u \\ 0 & 1 \end{bmatrix}, \quad \text{where } u = \frac{p-t}{1-t}.$$

Conversely, if $p < t$ then

$$\mathbf{P} = \begin{bmatrix} 1 & 0 \\ v & 1-v \end{bmatrix}, \quad \text{where } v = 1-\frac{p}{t}.$$

By a similar process we may construct a 3×3 transition matrix **Q** for the parents. For this we assume that the probabilities of transition in the two parents are equal and independent. First, we construct for either parent a 2×2 matrix, **R**, which is analogous to the matrix **P**. Thus, if $q > t$ then:

$$\mathbf{R} = \begin{bmatrix} p(R_m|R_t) & p(L_m|R_t) \\ p(R_m|L_t) & p(L_m|L_t) \end{bmatrix} = \begin{bmatrix} 1-u & u \\ 0 & 1 \end{bmatrix}, \quad \text{where } u = \frac{q-t}{1-t}.$$

From **R** we may construct a 4×4 matrix **U** for which each element is $p(H_m \times H_m|H_t \times H_t)$, by Kronecker or Hadamard multiplication of **R** with itself:

$$\mathbf{U} = \mathbf{R} \otimes \mathbf{R}.$$

However, since we are not distinguishing $R \times L$ from $L \times R$ matings, **U** may be collapsed into the 3×3 matrix **Q**, the middle element of which is $p(R_m \times L_m|R_t \times L_t)$.

Given **P** and **Q**, we may then easily calculate **M** from **T** by the equation:

$$\mathbf{M} = \mathbf{Q} \,.\, \mathbf{T} \,.\, \mathbf{P},$$

where . indicates ordinary matrix multiplication.

A similar process may be used for the cases in which there are two or more children from a particular mating, the assumption being that the same transition matrix may be applied independently for each child.

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