Handbook of Neuropsychology, Vol. 6: Child Neuropsychology
I. Rapin and S.J. Segalowitz (Vol. Eds)
F. Boller and J. Grafman (Series Eds)

CHAPTER 6

The genetics of handedness, cerebral dominance and lateralization

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> 'The fact that left-handedness 'runs in families' has . . . attracted the attention of many observers, yet the method of inheritance has not been fully studied. Many people imagine the condition to depend entirely upon training or imitation. There is thus much of guesswork concerning the true nature of the condition'.
>
> Ramaley (1913), p. 730.

Introduction and background

Handedness has a double importance to neuropsychology. Within a year or two of Broca's crucial discovery of the typical lateralization of language within the left hemisphere of the brain there were reports of patients in whom the converse was the case, and it became apparent that left-handedness was a modulating variable in the relationship (see Harris, 1991); and as one of us has described in an earlier volume of the present series, there is now little doubt that the cerebral specialization of left-handers is different from that of right-handers (Bryden, 1988). Handedness is however not only important as a secondary variable for interpreting other processes, but also is a major neuropsychological phenomenon in its own right which requires explanation and study. Indeed several reasons argue for handedness being a focal point for current neuropsychological research: it is one of the very few functional cerebral polymorphisms; it is readily, straightforwardly and efficiently measured in large numbers of normal individuals; and there is compelling evidence for some genetic control, therefore making it suitable for attack with the powerful tools of molecular genetics, and thereby allowing the unravelling of its neuro-developmental and cellular processes.

In this Chapter we will firstly review the evidence suggesting that handedness is indeed under genetic control (and will briefly assess the possible role of non-genetic factors), and we will then give an overview of the major genetic models that have been proposed, with particular emphasis on the currently most plausible models. In addition, we will consider the inheritance of a number of other behavioural asymmetries, and will discuss whether similar phenomena can be found in animals, and if so whether they may form an adequate model of human handedness. Finally we will consider the problems of localising within the genome a gene (or genes) for human handedness, and will look towards the future and consider the possible benefits that would arise from finding and sequencing the gene.

Defining the phenotype

Handedness is deceptively simple and deceptively complex to define. At first sight there seems little problem, 90% of the population readily replying 'Right-handed' to a simple question such as 'Are you right- or left-handed?'. However more sophisticated studies, dating back to Humphrey (1951) and Gillies, MacSweeney and Zangwill (1960), suggest that handedness is a more complex phenomenon. Although scientifically useful there is nevertheless a strong argument for following Peters' (1990) argument that "It is best, as Wittgenstein suggests, to begin with a simple common understanding of a concept before launching into elaborate definitions". In the final analysis it seems to us that the everyday notion of handedness encapsulates one of the central phenotypic truths concerning handedness. We will therefore comment briefly on the measurement of handedness at this stage, and will return to the question later when the genetic models have been described.

The measurement of handedness

Handedness can be defined and measured in two separate ways, according to the emphasis upon *skill* or *preference*. Preference is assessed by asking which hand is preferred for particular tasks, or observing which hand is actually used for carrying out a particular task; skill asymmetry is measured by comparing the ability of the right and left hands on the same task, such as peg moving. Preference and skill asymmetry are usually strongly intercorrelated, those preferring their right hand for tasks also tending to be more skilled with it. The relationship is strongest with complex, highly skilled tasks (such as writing), is less strong with less skill (such as moving pegs, or tapping fingers), and for tasks requiring little skill (such as grip strength) there is usually a minimal difference between the hands. Ascertaining the causal relationship between skill and preference is difficult (Morgan and McManus, 1988), since preference might be prior (preference causing greater practice and hence superior performance) or skill may be prior (skill asymmetry causing a preference for the more skilful hand). A recent study of children with autism, who show population level asymmetries for hand preference but not for skill asymmetry, suggests that preference may be prior to skill asymmetry (McManus, Murray, Doyle et al., 1992). Finally it should be noted that the reliability of preference is usually higher than for measures of skill asymmetry, such as the Annett peg board.

Handedness inventories

Preference is routinely measured by handedness inventories, which ask about the hand used for a number of unimanual tasks, typically on a three- or five-point scale; most widely used are modified versions of the Edinburgh Handedness Inventory (Oldfield, 1971). Other inventories include those of Annett (1967), Bryden (1977), Coren, Porac and Duncan (1979), and Crovitz and Zener (1962). Factor analysis usually shows that most of the variance is due to a single dimension, although some reports suggest that scales may be multi-dimensional (Healey, Liederman, and Geschwind, 1986; Steenhuis and Bryden, 1989).

Laterality indices: direction and degree of handedness

Laterality inventory responses are usually combined as a Laterality Index (LI), often scaled so that a pure right-hander scores $+100$ and a pure left-hander scores -100, with zero indicating ambidexterity. Distributions of LI are usually bimodal, most subjects having positive scores and a lesser mode showing negative scores, with few subjects scoring around zero. This bimodal distribution makes problems for defining handedness and for its statistical analysis (McManus, 1983). Two independent scores can readily be extracted. *Direction* of handedness, which correlates will with writing hand, considers subjects with positive scores ($LI > 0$) as right-handers and those with negative scores ($LI < 0$) as left-handers. *Degree* of handedness, the extent to which subjects are weakly or strongly handed, irrespective of direction, is measured as the absolute value of the laterality index, $|LI|$. Direction of handedness cor-

responds to the everyday notion of handedness; however degree of handedness is also important as it contains a substantial amount of the variance in a laterality index.

The following genetic analyses will begin by using a commonsense notion of handedness, taking at face value the multifarious approaches to the description of handedness of the many studies, and for our purposes generally accepting the dichotomous classification which is closest to the commonsense definition. We will therefore defer detailed discussion of phenotypics until later, when we consider the differences between the Annett and McManus genetic models.

Family studies of handedness

Genetic models for any phenotypic characteristic are tested according to their ability to fit certain types of data sets. For discrete, categorical characteristics such as handedness, the most important are the phenotype of offspring in relation to that of parents, and the phenotypes of pairs of monozygotic and dizygotic twins. Additionally it must be ascertained whether mating between phenotypes is random or assortative (i.e., like marrying like), and whether there is evidence for maternal or paternal effects, or for sex-linked effects, in which the probability of a phenotype depends upon the sex of the parent transmitting the characteristic or upon the sex of the offspring. In this Section we summarise results for all those studies which we have been able to find in the literature.

Table 1a summarises the combined results of 25 studies in which offspring handedness is tabulated against parental handedness[1]. Fig. 1 shows the individual data points on which Table 1a is based, ignoring differences between the sexes. A problem encountered in most studies is that all children from a family are typically treated as independent offspring; this means that if two children are right-handed from R × R parents then they are entered separately in Table 1a. Strictly speaking, however, they are not statistically independent, since they are more closely related to each other than to other individuals in the same column. Properly the data should be reported according to the number of left-handed siblings present in sibships of size 1, 2, 3, etc., as has been done by McManus (1985a); and, in the strictest sense, models should be fitted to entire pedigrees for individual families. The result is that statistical tests for homogeneity are only approximate, and formal model testing is less powerful than if complete family data are used. Finally it is worth noting that more powerful model testing would also be available if complete pedigrees were used, as in

[1] The studies surveyed are those of Ramaley (1913); Chamberlain (1928); Rife (1940); Merrell (1957); Annett (1973); Ferronato et al. (1974); Mascie-Taylor (1975); Chaurasia and Goswani (1977); Bryden (1979); Annett (1978); Coren and Porac (1980); Carter-Saltzman (1980); McGee and Cozad (1980); Leiber and Axelrod (1981); Ashton (1982); Spiegler and Yeni-Komshian (1983); Risch and Pringle (1985); McManus (1985a) (2 samples from study one, of the propositi and their sibs and of the parental families, and three from study 2, of the propositi and their sibs, of the maternal families, and of the paternal families); and the National Child Encephalopathy Study (NCES) (3 separate samples, of the propositi and their sibs, of the maternal families, and of the paternal families) — see McManus and Crow, 1990, unpublished).

The data of Chamberlain (1928) show minor inconsistencies and we have used the values calculated by Annett (1973). In the summary table we have not included the 'special families' collected by Chamberlain (1928) and Annett (1973) (in each case families with two left-handed parents collected by newspaper and radio appeals), since both include more left-handers than are found in randomly obtained subjects; thus in the Chamberlain data 25% of the 24 children of two left-handed parents in his primary sample were left-handed, while 53% of the 76 children in his added families were left-handed. The data of McManus (1985a; Crow and McManus, 1990) are here reported by sex of parents and offspring. The data of Bryden (1979) are reported in preference to those of Bryden (1982) which, although slightly more extensive, do not divide offspring by sex. The data from the National Childhood Encephalopathy Study are previously unpublished data from a study by McManus and coworkers in the United Kingdom which looked at a national cohort of children with acute neurological illness between the ages of 1 and 3 years. Each child was matched with a sex-matched control in the birth register, and at the age of between 8 and 12 years the cases and controls were followed up. A questionnaire was sent to the parents asking about the handedness of the study child, the study child's siblings, the parents, each parent's siblings, and the grandparents of the study child. Data were analysed separately for each generation and each side of the family, and all individuals were included, with the single exception of the propositi with neurological illness, who had previously been shown to have a higher prevalence of left-handedness, presumably in part due to pathological factors.

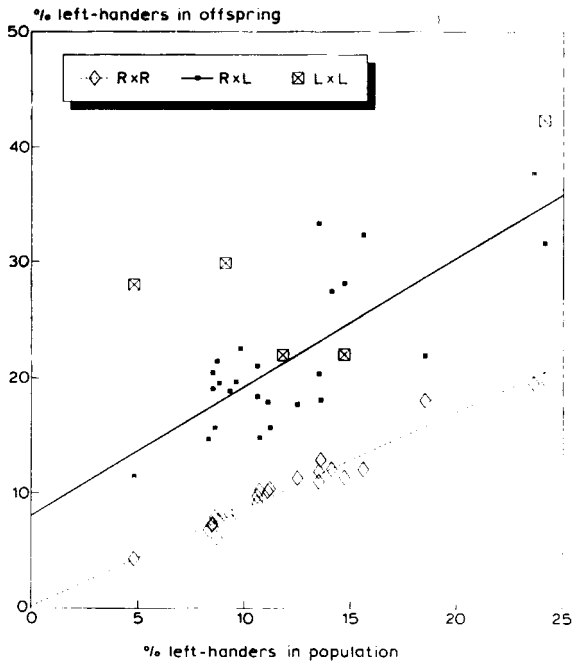


Fig. 1.: Handedness in offspring of R × R, R × L and L × L matings, in relation to the overall prevalence of left-handedness in the cohort. Offspring, parental and grandparental generations are plotted separately within studies, since the prevalence of handedness is typically different in each. Dotted and dashed lines represent best fitting linear regressions through the offspring of R × R and R × L matings respectively.

most linkage studies (e.g., Kimberling, 1983), although this has not been done in the handedness literature. Furthermore, it should be noted that Table 1a is only an approximate guide to the studies on which it is based, since the overall prevalence of left-handedness often differs substantially between studies.

Table 1a, based on 72,600 offspring from 25 sets of parent-child data, shows several clear findings requiring explanation by any convincing genetic model. Firstly, there is a clear familial effect upon handedness, the probability of a child being left-handed rising with the number of left-handed parents. Summing across studies, approximately 9% of the children of two right-handed parents are left-handed, compared with about 19% of the children of one left and one right-handed parent, and about 26% of the children of two left-handed parents. One left-handed parent therefore makes one 2.3-times more likely to be left-handed, and two left-handed parents make one 3.4-times more likely to be left-handed in comparison with two right-handed parents; and two left-handed parents make it 1.5 times more likely to be left-handed than a single left-handed parent. Nevertheless it should be noted that neither left-handers nor right-handers 'breed true'.

TABLE 1a

Handedness in families, according to maternal/paternal handedness and the sex of offspring

Not all studies gave results separately by sex of offspring, or differentiated R × L matings from L × R matings, and hence marginal totals are not sums of main table entries.

Parental handedness		Offspring		
Father	Mother	Sons	Daughters	Total
Right	Right	10.4% (30,268)	8.5% (26,020)	9.5% (63,250)
Right	Left	22.1% (1815)	21.7% (1688)	19.5% (8933)
Left	Right	18.2% (2308)	15.3% (2100)	
Left	Left	27.0% (215)	21.4% (168)	26.1% (417)

TABLE 1b

Handedness in families as given in Table 1a, except data are broken down by approximate year of birth of propositi

Parental handedness		Offspring		
Father	Mother	Sons	Daughters	Total
(1880 – 1939)				
Right	Right	6.0% (7214)	5.1% (4583)	6.1% (12,753)
Right	Left	14.9% (228)	23.5% (179)	18.8% (1104)
Left	Right	17.1% (298)	11.6% (232)	
Left	Left	35.1% (37)	33.3% (21)	40.9% (66)
(1940 – 1954)				
Right	Right	10.9% (16,028)	8.2% (13,721)	9.6% (33,153)
Right	Left	22.6% (954)	21.8% (806)	19.8% (4286)
Left	Right	18.7% (1107)	15.3% (953)	
Left	Left	26.3% (76)	22.6% (62)	25.5% (153)
(1955 – 1979)				
Right	Right	13.5% (7386)	11.1% (7716)	11.9% (17,344)
Right	Left	23.9% (633)	21.1% (703)	19.4% (3543)
Left	Right	17.9% (903)	16.3% (915)	
Left	Left	24.5% (102)	17.6% (85)	21.7% (198)

the implication is that neither right-handedness nor left-handedness is a classical Mendelian characteristic. Finally, and of great importance for the genetics of handedness, it must be noted that two left-handed parents have the surprisingly low prevalence of 26% of left-handedness in their children.

Although 7 of the 25 studies surveyed[2] failed to report whether it was the mother of father who was left-handed in R × L families, there is a strong suggestion that left-handed mothers are more likely to produce left-handed offspring than are left-handed fathers (see Table 1a). Log-linear modelling also shows that there is a higher prevalence of left-handedness in the children of R × L matings (21.9%) than in L × R matings (16.7%), making children 1.3 times more likely to be left-handed if they have a left-handed mother than if they have a left-handed father. Such a finding could result from a sex-linked or sex-related genetic effect, or from a greater social influence on the child likely to be exerted by the

[2] The 7 studies that do not distinguish between left-handed fathers and left-handed mothers are Ramaley (1913), Ferronato et al. (1974); Mascie-Taylor (1975); Chaurasia and Goswani (1977); Annett (1978); Carter-Saltzman (1980), and Leiber and Axelrod (1981).

mother. This question is discussed further below. There is also a suggestion in Table 1a of an interaction whereby the children of L × R matings have a higher prevalence of left-handedness in sons rather than daughters, but that the effect is almost absent in R × L matings. Table 1b, which subdivides the propositi according to their date of birth, suggests that the interaction is unstable, and probably therefore of little importance. In contrast the other sex differences are seen robustly in studies from all periods.

Assortative mating can complicate genetic models, and it is advantageous if it is absent. Table 2 summarizes data on the matings of the four different parental handedness combinations in the 17 studies for which data are available. Log-linear modeling by means of general linear modelling (GLIM) shows that there is no evidence that assortative mating is more frequent than would be expected by chance (the small association shown in Table 2 being due to the combining of independent tables with different marginal proportions). The potential complications of assortative mating for model fitting may therefore be ignored.

Twin studies of handedness

The study of monozygotic (MZ, identical) and dizygotic (DZ, non-identical or fraternal) twins is a conventional method for assessing the relative contributions of genetic and environmental factors. The method is often misunderstood, it being assumed that mere similarity or dissimilarity of MZ twins argues for genetic or environmental control respectively. In fact the critical analysis compares MZ twins (who have identical genes) with DZ twins (who share only half their genes); any *increased* concordance of MZ compared with DZ twins may then be attributed to genetic factors.

There have been many studies of the handedness in twins, although few have classified data as fully as is desirable; the study of Neale (1988) is a rare exception in the relative completeness of the reporting of its data. The data from 14 studies[3] of R-R, R-L and L-L pairs in MZ and DZ twins are summarised in Table 3. An important artefact applies to twin data collected before 1930 (and hence they have been omitted from Table 3). Although the genetics of blood groups was discovered by Landsteiner (1900) for several decades after that the classification of twin pairs still relied principally upon physical appearance. While questionnaire methods concerning physical appearance can be a valid method of twin-typing (Cederloef, Friberg, Jonsson et al., 1961; Torgersen, 1979), physical appearance was not used in a valid way before 1930, since many workers believed that MZ twins showed 'mirror-imaging', in which each twin was the enantiomorph of the other, due to fission from a single fertilised ovum. Right-handedness in one twin and left-handedness in the

TABLE 2

Frequency of different mating types in handedness studies

Paternal handedness	Maternal handedness		
	Left	Right	Total
Left	75	656	731
Right	556	7762	8318
Total	631	8418	9049

TABLE 3

Frequency of different handedness combinations in monozygotic and like-sexed dizygotic twins

Handedness	Monozygotic	Dizygotic
R-R	2184	1951
R-L	629	585
L-L	87	53
Observed/expected discordant pairs	0.901	0.993

[3] The twin studies surveyed here are those of Wilson and Jones (1932); Stocks (1933); Newman et al. (1937); Rife (1940); Rife (1950); Zazzo (1960); Carter-Saltzman et al. (1976); Loehlin and Nichols (1976); Springer and Searleman (1978); McManus (1985, NCDS); Neale (1988), and several studies cited by Zazzo (1960), including his own and those of Bouterwek in 1938, Thyss in 1946, and Dechaume in 1957.

other twin was therefore used as evidence for monozygosity, meaning that the classification of handedness and of zygosity were not independent (McManus, 1980).

Taken overall it can be seen from Table 3 that there is a slightly lower rate of discordance in MZ twins (21.7% of 2900 pairs) than in dizygotic twins (22.6% of 2589 pairs). That however is not a powerful comparison since in most studies the prevalence of left-handedness is not identical in MZ and DZ twins (and is higher in MZ twins in 9 of the 14 studies). A better method is to compare, separately for each twin type in each study, the observed number of discordant pairs as a proportion of the number expected under a binomial distribution. In 13 of the 14 MZ studies there are fewer discordant pairs than expected, averaging 90.1% of the expected number, whereas in DZ twins only 6 of 14 studies show fewer discordant pairs than a binomial expectation, the observed numbers averaging 99.3% of the expected. Thus, overall DZ twins do not differ from binomial expectations, whereas MZ twins show more concordance than would be expected. These data therefore undoubtedly suggest that there is a genetic contribution to handedness. However the absolute size of the effect is small, and an adequate genetic model must therefore not only account for the greater concordance of MZ than DZ twins, but must also explain the low overall concordance in MZ and DZ pairs. It should be noted that low concordance does not imply that the remaining variance is environmental — it could also be the result of measurement error, or of irreducible noise (see the Section on the biology of asymmetry, p. 124).

Adoption studies

Characteristics often run in families. However the fact that offspring are similar to parents is not convincing evidence of a genetic component, since parents also transmit a particular environment to their offspring (and in the case of phenotypes such as wealth it is readily apparent that rich parents have rich children principally because of environmental or cultural transmission). The transmission of genes *can* be distinguished from the transmission of environment by means of adoption studies. Surprisingly there have been few such studies of handedness. Since the direction of handedness is normally fixed at a fairly early age it is necessary that adoption should also take place early (and hence little useful information can be gained from studies such as that of Hicks and Kinsbourne (1976), which looked at the step-children of divorced and re-married parents, where exposure to the non-biological parent was at an average age of 13 years, and that of Longstreth (1980) in which the average age of adoption was 7.6 years). The literature contains only two adequate studies of adoption, one of which has not yet reported data on children at a late enough age for handedness to be fixed (Plomin and DeFries, 1983; Rice, Plomin, and DeFries, 1984). In the other study, that of Carter-Saltzman (1980), which only used a partial adoption design, the handedness of 415 adopted children showed no similarity with their adoptive parents, whereas the handedness of a control group of children showed a significant correlation with the handedness of their biological parents. Although larger and better adoption studies would be desirable, the present evidence is compatible with handedness being under genetic control.

Chromosomal studies in handedness

We are unaware of any systematic studies searching for chromosomal or karyotypic errors in left-handers. Left-handedness is more common in individuals with Down's syndrome (trisomy 21), but this is not due to a specific association with the abnormality (Batheja and McManus, 1985), but instead reflects a generally higher prevalence of left-handedness in mental retardation (Pipe, 1988, 1990).

Other data

Genetic models of handedness must not only account for the specific data associated with familial and twin associations, but must also be compatible with other general properties associated with han-

dedness. A meta-analysis by Seddon and McManus (1990) of the prevalence of left-handedness in 100 populations involving 284,665 subjects found an overall prevalence of 7.78%, a value very close to that found by Coren and Porac (1977) who reported that 7.4% of 1180 works of art produced during the past five millenia portrayed unimanual hand usage with the left hand. The prevalence is however somewhat lower than the 10.8% observed in the 25 studies summarized in Table 1a.

Despite some earlier reports which had suggested that there were secular trends in the prevalence of left-handedness (e.g. Levy, 1976), Seddon and McManus did not find evidence of a higher prevalence of left-handedness in more recent studies, although sinistrality was significantly less common in studies with older subjects. However age and year of birth are highly correlated across studies and it was not therefore possible to reject the possibility that year of birth may be a better correlate of sinistrality than age. There was also a significant tendency for the prevalence of left-handedness to be higher in smaller studies.

Seddon and McManus (1990) found a higher prevalence of left-handedness in males (8.52%) than in females (6.69%), the difference being shown in 83% of 63 studies. The size of the sex difference showed no significant association with any of the other variables measured.

A recurrent finding in family studies of handedness (see McGee and Cozad, 1980) is a higher prevalence of left-handedness among offspring than among parents; and indeed the effect was noted by Ramaley (1913), who called it 'a manifest absurdity'. It represents a potential problem for genetic theory if it implies a failure of the Hardy-Weinberg equilibrium. Although partly due to reporting biases, because of children inaccurately describing their parents' handedness (Porac and Coren, 1979), that alone cannot account for the finding since, as Ashton (1982) points out, the effect is present in his study (and also in the ICM2 study of McManus, 1985a), in which parents and offspring report their own handedness. Additionally the effect is present in the National Childhood Encephalopathy Study (NCES), in which parents reported the handedness of their children (see McManus and Crow, 1990). The effect is not readily explained by possible secular trends, which are typically suggested as topping out in recent decades (Levy, 1976), whereas the parent-offspring differences continue to be found in very recent data. Furthermore, as Ashton (1982) points out, if the effect is merely the result of secular trends, and if the effect has been present for a century or more (the parents in the study of Ramaley (1913) being born in about 1870), then far larger changes in left-handedness prevalence should be apparent than are actually found. Since meta-analysis (Seddon and McManus, 1990) suggests that reported left-handedness decreases with increasing age, that might explain the phenomenon. At present we can do no better than to reiterate the view of McGee and Cozad (1980, p. 267) "that left hand preference over the lifespan is diminished, at least to some degree, by socialization and/or cultural pressures to the contrary".

Non-genetic effects: birth stress, family size, etc

Many investigators have studied the association of a range of environmental influences upon the prevalence of left-handedness. Causality can be difficult to assign (as with obstetric factors, in which most investigators suggest that birth complications cause left-handedness, although Geschwind and Galaburda (1987, p. 176) have argued that left-handedness and birth stress are both caused by some third process). In this Chapter it would be inappropriate to dwell at length upon all possible environmental factors, and instead we will briefly comment on a few of importance and refer the interested reader elsewhere. At present we remain to be convinced, even if environmental factors do have causal effects upon left-handedness, that those effects are anything other than small, accounting for only a tiny proportion of cases.

Birth order

Birth order effects are important in attributing environmental origins to phenotypes since genes gen-

erally cannot know the order in which they will be born, and hence cannot explain such effects. An influential paper by Bakan (1971) suggested that left-handedness was particularly common in first-born and fourth or later-born children. The many studies since then have been reviewed in a meta-analysis by Searleman, Porac and Coren (1989) who concluded that they "found no evidence to relate birth order position to deviations from right-sidedness" (p. 397).

Parental age

Coren (1990) reported that left-handedness increased with maternal age, mothers over 40 being twice as likely to have left-handed offspring compared with 17 – 24-year-old mothers. However, as McManus (1990) has commented, the effect was not observed in the much larger and more representative sample analysed by McManus (1981).

Birth stress

Bakan's (1971) explanation for his birth order effect was that left-handedness was the result of anoxia secondary to obstetric complications, which are more common in first-born and later-born children. Many studies have subsequently looked at birth stress and left-handedness, although most are retrospective, with all the potential complications that that involves. Large-scale prospective studies, such as that of McManus (1981), which examined the 12,000 births in the British National Child Development Study (NCDS) found no evidence for a relationship between obstetric factors and sinistrality. The meta-analysis of Searleman et al., (1989) concluded that there was some marginal evidence for birth complications resulting in left-handedness, although the effect acounted for far less than 0.1% of the variance. Despite the strongly argued case of Bakan (1990), we feel that the more circumspect conclusion of Schwartz (1990) is probably correct.

Pathological left-handedness

The concept of pathological left-handedness dates back principally to the work of Gordon (1921), although hints of it may be found earlier. It is a controversial topic, in part because its definition is not clear, and in part because there have been few direct tests of the presence of left-handedness within children who have received definite brain damage at a vulnerable age. There have, however, been indirect attempts to assess its prevalence, principally in the work of Satz (e.g. Satz, 1972; Satz, Orsini, Saslow et al., 1985; Soper and Satz, 1984). Summaries of the problem and of the controversy may be found in McManus (1983b) and Harris and Carlson (1988). The difficulty of assessing the magnitude of the phenomenon is seen from a consideration of the definition: children who are hemiplegic and as a result cannot use their right hand are undoubtedly left-handed of necessity, their skilled performance with the left hand being superior to that of their (hemiplegic) right hand, but there is no strict sense in which they have expressed a preference for use of the left hand — they use it, *faute de mieux*, as would an aplasic or an amputee, because they have no choice. The best summary of a complex literature is perhaps that if it does exist, pathological left-handedness is certainly not a common or a major cause of left-handedness, at least in the normal population without apparent brain damage, and it may even be rare within known brain-damaged populations.

Specific genetic models: I. Conventional Mendelian models

The early history of genetic modelling of handedness is characterised by conventional Mendelian models, in which a small number of alleles is directly related to a small number of phenotypes, specific alleles being in a one-to-one relationship to specific phenotypes, just as in Mendel's genetic model of the pea one allele when homozygous produced smooth peas and the other produced wrinkled peas. Such genetic models of handedness invariably fail, because they do not take account of the unusual biology of asymmetric characteristics. Here we briefly review the models that have been proposed.

The earliest formal genetic model of handedness was that of Ramaley (1913), who pointed out that

Jordan (1911) had published several pedigrees of left-handedness and suggested that left-handedness was inherited as a recessive trait (although as Jordan himself admitted, the evidence of family trees was far from compelling). Ramaley concluded that left-handedness was indeed a classic Mendelian recessive trait, with two alleles, R and L, such that those of genotype LL are left-handed, and those of genotype RR or RL are right-handed. Ramaley recognised that the model makes the strong prediction that two left-handed individuals, each necessarily of genotype LL, can only produce LL offspring, who must all be left-handed. In the 305 families he studied, only two were of type L × L; and although in one family all four children were left-handed, in the other only two out of three were left-handed. Ramaley recognised the seriousness of this single errant child, and comments: "It is possible that one of the parents . . . was naturally right-handed and the left-handedness was only acquired. If that is not the case then there seems to be no explanation to offer for the appearance of the right-handed child". Examination of our Table 1a shows that the errant child was by no means atypical, and hence that the recessive model must fail.

Subsequent attempts to salvage a single locus recessive model invoked differences between the sexes (Chamberlain, 1928), partial penetrance in the homozygous recessive (Rife, 1950; Trankell, 1955) or mixed handedness in heterozygotes (Annett, 1964). Additionally Levy and Nagylaki (1972), tried using two alleles at each of two loci, one pair, *L* and *r*, determining the hemisphere dominant for language, and the other pair, *C* and *i*, controlling whether hand dominance was ipsilateral or contralateral to the dominant language hemisphere. Although there has been controversy over fitting the model (see Hudson, 1975 and Levy, 1977), the Levy-Nagylaki model ultimately fails, as does also the Annett (1964) model, because it fails to fit the twin data. Since each genotype is associated specifically with right or left handedness (or mixed handedness for Annett, 1964), then handedness must be identical in MZ twins who have the same genotype. However Table 3 shows that is clearly not the case. The point has been made clearly for the Levy-Nagylaki model by Corballis and Beale (1976) and by Morgan and Corballis (1978).

In general the above models are all characterised by assigning one allele for each major phenotype, so that homozygotes produce particular phenotypes. Put generically, RR produces right-handedness and LL produces left-handedness. Partial penetrance may be allowed for some or all genotypes, but ultimately the models require particular genes to produce particular asymmetric phenotypes. The important insight of genetic modelling in the 1970s was that the biology of lateralisation means that such models, which we may term *symmetric*, are implausible since asymmetry cannot arise in biological systems in such ways. Recent models instead draw heavily on the biology of asymmetry and are *asymmetric* in the sense that one allele does not produce the mirror-image effect of the other; the models are intrinsically asymmetric.

The biology of asymmetry

The modern view of the central role of biological processes for understanding the genetics of handedness and cerebral dominance is principally due to the influential papers of Morgan (1977), Morgan and Corballis (1978) and Corballis and Morgan (1978). These authors approached the problem of lateralisation from a different perspective, and reviewed a range of data from the biological literature which suggested the existence of a range of innate lateralities. The authors were impressed by the low concordance in handedness between siblings, but simultaneously accepted that handedness undoubtedly ran in families, concluding that "the data might be reconciled by supposing that there are indeed systematic differences *between* families, but that the distribution *within* families is essentially binomial" (Morgan and Corballis, p. 275). Impressed also by evidence for the existence of a left-right spatial gradient within organisms, and perhaps in the structure of the oocyte, and by the argument *a priori* that

genes are essentially left-right agnosic, that is, they cannot code for asymmetries in any direct fashion, Morgan and Corballis argued that

> "genes do not, perhaps cannot, encode the direction of a structural asymmetry. Rather, genetic factors may serve to 'buffer' an organism against asymmetrical nongenetic influences, or conversely, to permit some nongenetic asymmetry to be expressed. Thus genetic variation may influence the degree but not the direction of asymmetry";

and they concluded,

> "There is in fact very little evidence that genetic variation plays any significant role in causing variations in human laterality". (Morgan and Corballis, 1978, p. 276.)

The analysis of Morgan and Corballis has been influential, but is almost certainly wrong. Its error, of assuming that all lateralities derive from a single right-left gradient which is implicit in the biology of the organism, is readily seen from a consideration of individuals with *situs inversus*, in which the viscera are mirror-imaged (so that the heart is on the right, the liver on the left, etc); if these individuals have a reversed left-right gradient then that gradient should also cause the individuals to be left-handed (or alternatively if they have no gradient, and chance alone has rendered them reversed then half of them should be left-handed). In fact the prevalence of left-handedness in *situs inversus* is the same as in the rest of the population who have *situs solitus*, Torgerson (1950) reporting a prevalence of left-handedness of 6.9% in 160 individuals. Nevertheless, despite the flawed conclusion of Morgan and Corballis there is little doubt that their central premise that laterality is essentially a biological process, and should be analysed in a biological fashion, is indubitably correct, and influenced theorising in the 1980s.

A central theoretical point, which elsewhere we have called 'Morgan's Principle', is Morgan's (1977) contention that genes are left-right agnosic. The conclusion derives principally from Immanuel Kant's consideration of the impossibility of a remote observer being able to distinguish enantiomorphic (mirror-image) objects except by comparison with some other enantiomorphic reference object. Since genes are inherently unidimensional, being linear strings of base-pairs, they cannot code mirror-symmetric information within their structure, so that enantiomorphs may only be distinguished in comparison with an asymmetric reference — a cellular 'signpost' as it has been called (McManus and Mascie-Taylor, 1979). An extension of the principle is that since genes cannot code asymmetry within their structure it is also highly unlikely that allelic pairs, derived by mutation or transposition, could code mirror-symmetric products. The problem is of assembling appropriate DNA sequences coding for proteins with mirror-symmetric tertiary structures. Since proteins are constructed of enantiomorphic building blocks (amino acids), and tertiary structure occurs due to spontaneous folding of the amino-acid chains, then the base-pair sequences for enantiomorphic proteins will be utterly unalike. No simple mutation or transposition will therefore produce one sequence from the other. Because of this biological principle, none of the genetic models considered so far is likely to fit the data on handedness, since all contain alleles producing mirror-symmetric effects.

Although Morgan's principle seems to be valid for proteins, Holliday (1990) has argued that it may not also be true for the tertiary structure of RNA molecules, although the possibility has not yet been fully evaluated.

An alternative view of asymmetries is that they are affected by what are essentially random processes (Annett, 1978, 1985a; McManus, 1979, 1984, 1985a). Organisms are complex assemblies of very many cells, all approximately distributed around a mid-line. Cell growth and division is inherently fallible, and hence although the two sides of an organism will contain similar numbers of cells, it is statistically highly unlikely that they will contain identical numbers of cells. Half of a group of organisms will therefore have more cells on the left-hand side and half will have more on the right-hand side. Such differences explain the small but measurable asymmetries in characteristics such as incisor thickness. Known

as 'fluctuating asymmetry', it is of necessity not under genetic control, and fluctuates randomly from generation to generation. It can vary in magnitude between individuals due to 'biological noise' (such as heat, cold, stress or radiation), which makes developmental errors more likely, and increases the total variance in the population (see, e.g., van Valen, 1962; Siegel and Doyle, 1975; Soulé, 1982; Soulé and Cuzin-Roudy, 1982). Fluctuating asymmetry can result in unilateral characteristics if each side secretes a substance inhibiting the growth of contralateral cells, positive feedback meaning that whichever side becomes marginally larger will then grow disproportionately larger until the structure persists only on that side — a process of 'canalisation'. Because of fluctuating asymmetry the biological baseline for assessing asymmetry is not a population in which one form or other predominates, but a population in which half are dominant on one side and half are dominant on the other. If 50% of the population were left-handed (or, indeed 50% of the population had their heart on the left side) then neither phenomenon would be of particular biological interest. It is the presence of directional asymmetry (a ratio other than 50:50) that makes their biological analysis both difficult and challenging.

Although fluctuating asymmetry is by definition not under genetic control, its presence or absence can be. Consider a system in which there is a directional asymmetry under genetic control (such as the heart being on the left of the body in most humans). There is necessarily a complex control process which results in that asymmetry. If it should be disrupted, perhaps by a genetic mutation in one of the proteins controlling it, then the resulting phenotype will not be a reversed asymmetry but will be fluctuating asymmetry. There will therefore be two allelic variants, one of which produces only fluctuating asymmetry and the other of which produces directional asymmetry. The fluctuating asymmetry therefore appears to be under genetic control (although strictly there is a complete absence of control which is resulting in fluctuating asymmetry).

An important and influential finding was the discovery and breeding of an inbred strain of mice containing a recessive gene known as the *iv* mutation, in which in its homozygous form *(iv/iv)* exactly half of the mice show *situs inversus* and the other half show *situs solitus* (Layton, 1976). The *iv* mutation is the clearest and most analysed example of genetic control of fluctuating and directional asymmetry by paired alleles (Bruckner, D'Eustachio and Horwich, 1989), and it follows on earlier work which had implied similar genes in other species (e.g., Tihen, Charles and Sippel, 1948; Baker-Cohen, 1961).

Taken together these three biological principles lay the foundation for our modern understanding of the genetics of handedness and lateralisation in general, and provide a complete and clear break between those genetic models which take them into account and those earlier models which were developed independently of them.

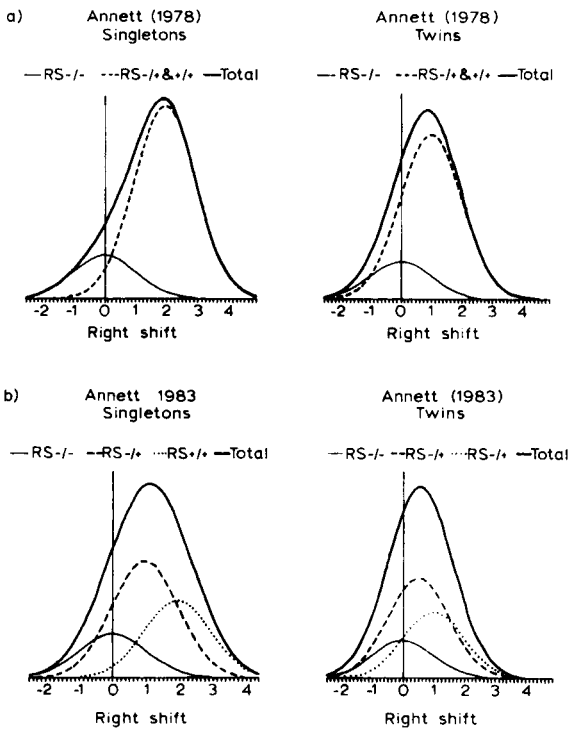
Specific genetic models: II. Models incorporating fluctuating asymmetry

During the 1970s both Annett (1978) and McManus (1979) independently developed genetic models which explicitly took as their central foundations that genetic models of handedness must contain random components reflecting the biological importance of fluctuating asymmetry. The models contain some similar components, although they differ in many of their details, and evolved under entirely separate influences; the models will first be described separately and will then be compared in their predictions and underlying assumptions. The strength of both models is that by invoking fluctuating asymmetry they solve two puzzles of the genetics of handedness. Firstly, by setting a ceiling of 50% on the possible prevalence of left-handedness in any population, they explain the seemingly low rates of left-handedness in the children of two left-handed parents. Secondly, they solve the problem of the discordance of monozygotic twins, since if fluctuating asymmetry is completely random (and may in the end be reducible merely to quantum noise) then two MZ twins showing fluctuating asymmetry will manifest independent chance events, and hence

discordance is to be expected (in just the same way that if a pair of MZ twins each tossed a coin we would also expect discordance in the outcomes).

Annett's 1978 model

Annett (1978) published a genetic model of handedness which was radically different from the earlier model published in 1964. Its development is described in Annett (1985a). In her 1978 monograph, Annett proposed that there were two distributions of manual ability, with similar variances but with different means, the system being under the genetic control of two alleles, RS+ and RS−. The RS+ gene was dominant to the RS− gene, and the genotypes RS+/+ and RS+/− both had a shift of their normal distribution to the right (hence the *R*ight *S*hift gene), and as a result a majority were right-handed. The RS−/− genotype did not produce a shift to the right and, as in animals, the distribution was centered at zero so that about half of such individuals would be expected to be left-handed. Since there is, in Annett's model, no strict



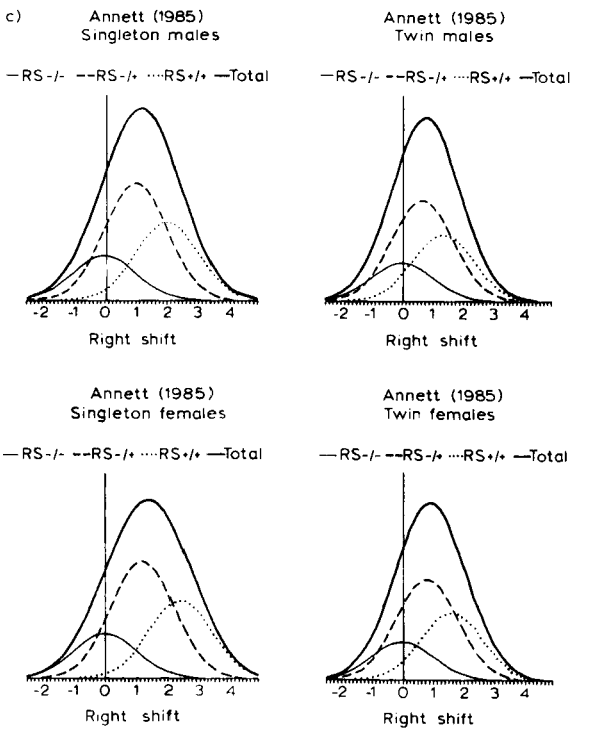


Fig. 2. The phenotype distributions of the RS−/−, RS−/+ and RS+/+ genotypes, as proposed by Annett in the three versions of her model: (a) Annett (1978), (b) Annett (1983) (as described in Annett and Kilshaw, 1983); and (c) Annett (1985a). The 1978 and 1983 models hypothesise that twins and singletons show different distributions, and the 1985 model also proposes that males are different from females.

criterion for left-handedness, the model then allowed a variable criterion (akin to the criterion in signal detection theory) so that individuals above the criterion were right-handed and those below were left-handed. Fig. 2a shows a diagrammatic summary of the model. Because of the presence of a variable criterion for left-handedness, the Annett model is not easy to fit since there are several free parameters. Annett circumvented this problem by calculating the gene frequency not from handedness data but from entirely separate data obtained from studies of the prevalence of right-hemispheric language derived from studies of dysphasia, the assumption being that since RS−/− individuals show random cerebral lateralization they will also show random lateralization for language, and hence half of them

will be right-hemisphere dominant for language. Since 9.27% of a group of dysphasic patients showed right hemisphere language the frequency of the RS −/− genotype must therefore be 0.1854, and hence the frequency of the RS− gene must be $\sqrt{\cdot 1854} = 0.4306$. The dysphasia data also allowed estimation of the extent of the right shift in the RS +/+ and RS +/− groups relative to the RS −/− group (whose shift was *a priori* set at zero); the right shift was calculated as being 1.937 standard deviations. The model could then be fitted to family data, and Annett showed there was an adequate fit to five family studies, two of them using two separate criteria. Finally Annett fitted the model to data on twins, and this necessitated a further addition to the model such that the extent of right shift in MZ and DZ twins needed to be less than in singletons, at 1.00 standard deviations rather than 1.937. Such an ad hoc modification shift strikes one, as Annett herself put it, as "an unlikely and undesirable complication of the right shift theory" (1978, p. 14), although subsequently she has argued (e.g. in 1985) that in fact it represents a fundamental feature of the process of twinning.

Annett's 1983 model

This model, which was first described by Annett and Kilshaw (1983) is broadly similar to the 1978 model except for the important change that instead of the heterozygous RS +/− individuals being identical to the RS +/+ individuals (i.e. the RS + gene is dominant), the RS +/− genotype is assumed to be additive, manifesting midway phenotypically between the two homozygotes (i.e. with a right-shift of 1.937/2 = 0.967 standard deviations: in practice Annett and Kilshaw (1983) have used values of 1 and 2 standard deviations). Since 49% of the population are assumed to be heterozygotes the change has a substantive effect upon the model. The 1983 model is outlined diagrammatically in Fig. 2b, making the assumption that in twins the heterozygotes also appear midway between the homozygotes. The principal theoretical reason for the change in the model would appear to be the desire to find a heterozygote advantage which would explain the balanced polymorphism of handedness.

The Annett (1983) model underwent a further change in Annett (1985a) in which it is proposed (see Fig. 2c) that the right shift is different in males and females, so that it is 1 and 2 standard deviations in males, and 1.2 and 2.4 standard deviations in females (Annett, 1985a, p. 315), and in this form the additive model has been compared against a dominant version in which males and females respectively have shifts of 1.23 and 1.43 standard deviations (Annett, 1985a, p. 319). The 1985 model also alters the extent of the shifts found in twins, "if the extent of shift is hypothesised to be smaller in twins than the singleborn by 33%" (p. 330), a value which is said to be a 'guesstimate' (p. 334). That results in shifts of 0.66 and 1.33 for RS +/− and RS +/+ male twins and 0.80 and 1.60 for female twins (Annett, 1985a, p. 331; the value of 1.10 for female twins on p. 331 of Annett (1985a) is assumed to be a typographical error).

McManus' genetic model of handedness

McManus (1979) described a genetic model of handedness which was subsequently pubished in greater detail in McManus (1984, 1985a), which also included improved model fitting using maximum-likelihood procedures for estimation of the parameters. The development of the model was influenced principally by Morgan's concept of genes being left-right agnosic, by the work on the genetics of *situs inversus* by Layton (1976), and by Collins' (1968) work on the lack of genetic control of handedness in mice. The model involves two alleles at a single locus and simple phenotypes which correspond to the everyday descriptions of right, and left-handedness. The model takes fluctuating asymmetry as its starting point and assumes that in its homozygous form an allele called *C* (for Chance) causes no effective control over lateralisation, and hence fluctuating asymmetry was the true phenotype, so that exactly 50% of CC individuals are left-handed and 50% are right-handed. The other allele, *D* for Dextral, in its homozygous form, DD, results

in pure directional asymmetry so that 100% are right-handed and none left-handed. These alleles, as also with those of Annett (1978, 1985a), are not producing mirror-image phenotypes.

Fitting the model required solutions to two problems. First, the model as defined did not indicate how heterozygotes, DC, would manifest phenotypically; it was therefore assumed that between 0 and 50% of offspring would be left-handed (i.e. the range of the two homozygotes), and the precise proportion was left as a free parameter in the model. Second, although studies differ in their manifest prevalence of left-handedness, it is unlikely that such differences correspond to changes in gene frequencies, which are more likely to be constant across the populations studied. The model therefore distinguished between the manifest prevalence of left-handedness, regarded as specific to each study, and dependent upon such factors as the method of measuring handedness and the sampling procedure of the study, and a single true prevalence of left-handedness which reflected the underlying allele frequencies, assumed to be similar in each study population. Thus for various reasons one may expect an overestimation of the prevalence of left-handedness in some studies and an underestimation in others. The McManus model simply assumes that if manifest right-handedness is more common than true right-handedness it is due entirely to true left-handers manifesting as right-handers, and vice-versa for manifest left-handedness being more common than true left-handedness.

The model was fitted to all of the family and twin studies in the literature using maximum-likelihood procedures with two free parameters, the expression in heterozygotes and the true prevalence of left-handedness. The best fit was with heterozygotes being expressed exactly midway between homozygotes (additivity) and with a true prevalence of left-handedness equal to 7.75% (a value which subsequently was found to be remarkably close to that found in the meta-analysis of Seddon and McManus, 1990). The genetic model is summarized in Table 4a. It should be emphasised that, in distinction to the model of Annett, fitting the model did not require reference data on cerebral lateralization for language, and neither did it require different parameters for twins and singletons.

TABLE 4a

Summary of McManus' (1985a) genetic model of handedness

Genotype	% Left-handedness	% Right-language
DD	0	0
DC	25	25
CC	50	50
$p(C) = 0.155$		

TABLE 4b

The McManus (1985a) model with a sex-linked modifier, having an epistatic influence upon the expression of the DC alleles

	Percentage of left-handedness (or of right-hemisphere language) in each genotype:				
	Males		Females		
Modifier gene:	*M*	*m*	*MM*	*Mm*	*mm*
DC system					
DD	0	50	0	0	50
DC	25	50	25	25	50
CC	50	50	50	50	50
$p(C) = 0.1346$; $p(m) = 0.0452$					

Comparison of the Annett and McManus models

Although the Annett and McManus models are similar in many ways, and as McManus (1985a) has pointed out, if the parameters of the Annett model are chosen carefully then the two models can become almost indistinguishable in their predictions for family data, we wish to argue that the models do make different predictions and hence are distinguishable. Annett treats twins differently from singletons, while McManus does not, and Annett's model requires more arbitrary setting of specific parameters than does McManus'. McManus (1985a) compared the Annett and McManus models using a formal, maximum-likelihood procedure in fitting the same set of family and twin data; the

McManus model was a better fit to the data unless one allowed the Annett model to use parameters which seem implausible.

Phenotypics and the differences between the Annett and McManus genetic models

The seeming irrelevance of phenotypics often makes it feel less like modern science and more like mediaeval theology. Nevertheless correct phenotypics is a key precursor to correct genetic analysis, allowing one to 'carve nature at the joints', categorising biological processes non-arbitrarily to contain maximal useful variance and minimal noise. Inappropriate phenotypes obscure genotypes in a fog of random variation. Consider the case of phenylketonuria, an important cause of mental retardation. Many children have mental retardation, but only a minority have phenylketones in their urine. The latter sometimes have siblings with mental retardation who also have phenylketones in the urine; and that one in four siblings is affected, and neither parent is affected, supports an autosomal recessive model. Consider then the difficulty of unravelling the genetics without knowing that there were ketones in the urine. Phenylketonuric children are often fair-haired and blue-eyed; but so also are many other children, thereby introducing noise into the data; likewise the children may have retarded siblings, but perhaps for other reasons, such as trisomy 21. The likelihood of finding an autosomal recessive condition within such noise is nearly zero. This tale has both a moral and a twist. The moral is that since genes are biological, phenotypes must be biologically convincing rather than arbitrary. The twist is that understanding phenylketonuria has allowed molecular genetic analysis, which shows that instead of one phenotype there are actually eight (Tourain and Silbury, 1983). Understanding genetics and phenotypics is mutually interdependent, iteration eventually resulting in each being more accurate.

The McManus and Annett models differ principally, as has been recognised by McManus (1985b) and Annett (1986), in their conceptions of the phenotypics of handedness. The McManus model is straightforward in that it reflects the commonsense view of right and left-handedness as being two discrete categories, corresponding to the definiton of direction of handedness given earlier. Although right- and left-handers differ, there are no measurable differences in skill asymmetry between a right-hander with a DD genotype and a right-hander with a DC or with a CC genotype. Differences in degree of handedness, be they measured by preference or skill, do occur within both right- and left-handers, but they are not under genetic control (or if they are, it is a different locus from the DC system). The Annett model is more complicated. Handedness is seen as principally defined in terms of skill asymmetry, with preference being a secondary phenomenon, defined in terms of an arbitrary threshold or criterion. The distribution of skill asymmetry is composed of three separate normal distributions, corresponding to the RS −/−, −/+ and +/+ genotypes, the −/− genotype being centred at zero, and the other distributions being shifted to the right. The Annett model says that strong, medium and weak right-handers differ not only in their relative hand skill but also in their likelihood of being particular genotypes, the modal genotypes being RS +/+, +/− and −/− respectively. It is because of this difference that Annett and Manning (1990) can relate differences in skill to heterozygote advantage and hence to a balanced polymorphism. The Annett model predicts that weak and strong right-handers should differ in their prevalence of left-handed relatives, whereas the McManus model predicts no such differences: McManus (1979; Fig 2.12) found no difference in the proportion of left-handed relatives in relation to degree of handedness within handedness groups.

The Annett and McManus models of the phenotypic description of handedness differ principally in their conceptualisation of the distribution of the laterality index for skill asymmetry. Annett sees it as the sum of three normal distributions, one centred at zero and the other two shifted towards the right, whereas McManus sees it as a sum of two normal distributions, one to the right of zero and the other placed symmetrically to the left of zero, the 'sym-

metric bimodal' model of skill differences (McManus, 1985b). The differences between such models can readily be tested by fitting them to the peg-moving data of Annett and Kilshaw (1983), or to handedness data from the National Child Development Study. McManus (1985b) has carried this out using maximum-likelihood procedures, and finds clear evidence that the Annett model provides a less good account of the data. In reply Annett (1985b) has suggested that the right-shift distribution is not of skill per se but of a latent variable. If that is so then it no longer seems clear (as McManus [1985c] has pointed out) how the model can be tested against empirical data, and how it can be used to make the type of predictions made by Annett and Manning (1990).

Sex differences and the genetics of handedness

Neither the Annett nor McManus model originally considered sex differences, and neither model in its original form dealt readily with the two important pieces of evidence suggesting sex differences in the inheritance of handedness: the overall higher prevalence of left-handedness in males, and the stronger maternal effects than paternal effects upon offspring handedness.

Different sex-related expressions of the right-shift gene were introduced into her theory by Annett (1985a), arguing that on the basis of measurements of the difference of right and left hand skill in males and females, that the extent of the right shift in RS+/− and RS+/+ genotypes was greater in females than males, which would result in a greater prevalence of left-handedness in males than females. Naturally such a manoeuvre must readily explain the greater prevalence of left-handedness in males. It might also seem able to explain the maternal effect; as it is put by Annett (1985a, p. 327), "the RS model does predict a slight excess [of left-handed children born in R × L families]". However the effect is indeed slight, as is shown in Table 5a, in which for comparative purposes the Annett model is calculated for overall prevalences of left-handedness of 7.75% and 10.83% (the manifest prevalence in Table 1a); and left-handed offspring are expected to be 1.062 times more common in the offspring of R × L than in L × R matings, compared with the figure of 1.393× for the actual data of Table 1a.

Sex differences in the McManus model might be incorporated (as suggested by McManus 1985a, p. 17) through differential expression of left-handedness in the heterozygotes, the only part of the model not specified *a priori*. Different phenotypic expression in male and female heterozygotes (as might be expected if the dose-response relationship between gene number and phenotypic effect was slightly altered) readily produces different prevalence of left-handedness in the two sexes (Table 5b), but produced only a minimal maternal effect, R × L matings producing only 1.016-times more left-handers than L × R matings.

A novel model of the genetics of sex differences

Neither the McManus (1985a) nor Annett (1985a) genetic models copes well with sex differences. Each explains the excess of male left-handers only by the simple expedient of an extra parameter in the model. However, neither convincingly explains the maternal effect, and it seems probable that no single-locus autosomal model will explain it merely by tinkering with the phenotypic expressions in the sexes.

The idea of sex differences being due to a sex-linked gene for handedness has been toyed with by many investigators, but usually rejected because it would imply very large sex differences in overall prevalence. An alternative approach is to argue that the handedness gene is autosomal, but additionally a modifier gene is present on the X chromosome. Modifier genes act by turning off normally active genes, by processes such as methylation. It is of interest to note that modifier genes have been invoked elsewhere to explain the inheritance of Gilles de la Tourette's syndrome (Comings and Comings, 1986) and of the Fragile-X syndrome (Israel, 1987; Sherman, 1987).

How might a modifier gene act? The C allele when homozygous is normally without an action, merely allowing chance to act. Any modifier gene must

TABLE 5

Three genetic models of sex differences in handedness

(a) Annett (1985a): the right shift is 2.4 and 2.0 for RS+/+, 1.2 and 1.0 for RS+/− and 0 and 0 for RS−/− in females and males respectively, and the frequency of the RS− allele is 0.4306. (b) A modified McManus (1985a) model: the proportions of left-handedness in the DC genotype are 21.48% for females and 28.52% for males, and the frequency of the C allele is 0.155. (c) The modified McManus (1985a) model with a sex-linked modifier gene, as specified in Table 4b. Calculations are shown separately for an overall prevalence of left-handedness in the parents and offspring of 7.75% (i.e. as proposed by McManus (1985a) and found by Seddon and McManus, 1990), and 6.70% in parents and 10.83% in offspring, the particular prevalences found in Table 1.

Overall prevalence of left-handedness:					
Parents:		7.75%		6.70%	
Offspring:		7.75%		10.83%	
Father	**Mother**	**Offspring**		**Offspring**	
		Sons	**Daughters**	**Sons**	**Daughters**
(a) Annett (1985a) model					
Right	Right	7.47%	6.39%	10.69%	9.07%
Right	Left	13.17%	11.99%	18.27%	16.57%
Left	Right	12.52%	11.35%	17.41%	15.72%
Left	Left	21.53%	20.97%	28.86%	28.09%
(b) McManus model with differential heterozygotes					
Right	Right	6.72%	5.23%	10.11%	8.62%
Right	Left	19.59%	15.59%	22.39%	18.53%
Left	Right	19.26%	15.37%	22.08%	18.32%
Left	Left	30.64%	27.21%	32.96%	29.64%
(c) McManus model with a sex-linked moderator gene					
Right	Right	7.17%	5.24%	10.49%	8.63%
Right	Left	18.70%	16.67%	21.50%	19.55%
Left	Right	15.55%	14.46%	18.49%	17.44%
Left	Left	26.96%	25.92%	29.40%	28.39%

therefore inactivate D alleles, temporarily preventing them causing directional asymmetry, so that instead fluctuating asymmetry manifests. Consider a recessive modifier gene *m* (or its non-modifying co-allele, *M*), whose locus is the X chromosome. In *M* males and *MM* and *Mm* females the modifier will have no effect upon the normal expression of the DD or DC genotypes. However in *m* males, and *mm* females the modifier gene will inhibit the normal directional asymmetry of the DD and DC genotypes (although their D alleles will still be transmitted to offspring), and hence result in fluctuating asymmetry. The system is summarised in Table 4b. Since *m* males are more common than *mm* females the result is a higher prevalence of left-handedness in males; and in Table 5c the prevalence of the *M* allele has been chosen so that the overall prevalence of left-handedness is 27.4% higher in males than females, the overall value found in the meta-analysis of Seddon and McManus (1990). Thus far, the model, like those of McManus (1985a) and Annett (1985a) has merely explained one phenomenon by adding one extra parameter. However the modifier gene model also predicts a maternal effect. Female left-handers are more likely to transmit the C allele to their offspring than are male left-handers (since

more male left-handers will be genotypically DD but with the normal phenotype masked by the modifier gene), and hence their offspring are more likely to be left-handed. Table 5c shows that the maternal effect is more substantial than with the Annett and the McManus models, R × L matings producing 1.179 times more matings than L × R matings, a figure rather more compatible with the effect found in Table 1a, accounting for 46% of it, compared with 4% for the McManus model with differential heterozygotes and 16% for the Annett model. Formal maximum-likelihood fitting has not yet been carried out for the modifier gene model, although it does seem capable of explaining both the sex difference and the maternal effect for the addition of a single biologically reasonable parameter.

A relatively rare sex-linked modifier gene, altering the expression of a cerebral dominance gene, has interesting implications for understanding dyslexia, childhood autism and stuttering, all of which are characterised by an excess of males and an excess of sinistrals. If the sex-linked modifier not only altered the handedness gene but also acted on some other autosomal gene (normally involved in, say, reading or speaking) then it could explain the excess both of males and of left-handers in these conditions.

Handedness and cerebral dominance

Although this review is principally concerned with the inheritance of handedness, the association of handedness and cerebral lateralisation for language and other functions means that their inter-relationship must also be analysed. Comment is limited since there is little adequate data on the co-transmission of handedness and language dominance within families. Language dominance is best inferred from techniques that are not suitable for genetic epidemiological study — intracarotid sodium amytal testing, unilateral ECT, and the effects of unilateral brain damage. The only extant attempt to assess dichotic listening within families, Bryden (1975), is a useful start but does not have sufficient power to test or distinguish between models. Similarly the only study of language dominance and handedness in twins (Springer and Searleman, 1978) is too small for formal genetic analysis.

Genetic models of cerebral dominance are therefore restricted to explaining the association of handedness and language dominance within individuals, and cannot be regarded strictly as genetic qua genetic tests of the models in the absence of meiosis or recombination.

McManus' model for the association of handedness and cerebral dominance is straightforward. The model of handedness argues that the preferred hand is determined by a single pair of alleles, with a substantial chance element due to fluctuating asymmetry. The model of cerebral dominance for language (and for any other cerebral asymmetries due to the same gene) is similar; the DD genotype results in lateralisation typical for the characteristic (i.e. left hemisphere for language, right hemisphere for visuo-spatial functions, etc.) in all individuals, whereas the CC genotype results in chance allocation of functions to right and left hemispheres. Since chance allocation (in the DD and DC genotypes) is statistically independent for each characteristic, individuals of CC genotype will contain equal proportions of individuals with right-handedness and right-language, right-handedness and left-language, left-handedness and right-language, and left-handedness and left-language, whereas DD genotypes will all be right-handers with left-hemisphere language. Straightforward calculations for the model (McManus, 1984; 1985a) show that it predicts that 6% of right-handers and 29% of left-handers will show right-hemisphere dominance for language, figures compatible with estimates from dichotic listening and amytal studies. The model can be extended to explain the difference between acute and permanent aphasias (by invoking the presence of two separate language processing centres), and between handedness, language and visuo-spatial dominance (McManus, 1985a). Additionally the model is readily extended to account for observations such as those of Peters (1990), in which there is a suggestion that a substantial proportion of left-handers may be inconsistent in their handedness in the sense that they carry out some tasks such as

writing and tapping better with their left hand but are better with their right hand at carrying out other tasks, such as throwing, a dissociation which is rare in right-handers. If the different skills are controlled by separate cortical centres, both typically in the left hemisphere, then it can be predicted that 71% of left-handers but only 6% of right-handers would have throwing ability in the opposite hemisphere to fine motor skill (which is presumed to determine writing hand).

The genetic models of Annett (1978; 1985a) are more complex in their explanation of the association between handedness and cerebral dominance. Annett (1978) took the position that in the absence of the right shift both hand skill and language lateralization depend on chance; that model (i.e. the dominant form) therefore predicts that all RS+/+ and RS+/− genotypes will be left hemisphere language dominant, and that 50% of RS−/− genotypes will be left dominant and 50% will be right dominant. The proportion of right- and left-handers with right hemisphere language depends upon the specific threshold chosen for handedness. However, the model then makes clear predictions, so that when 8% of the population are left-handed, 7% of right-handers and 36% of left-handers show right-hemisphere speech. It is less clear how Annett's later additive model (1983) relates to cerebral dominance, although Annett and Manning (1990) imply that all RS+/− genotypes will be left-hemisphere language dominant by this model as well. Thus the specific predictions for the relation between handedness and language dominance are virtually unchanged.

Taken overall the two models both generally succeed in predicting the key data, of the proportion of right and left-handers showing right-hemisphere language dominance. McManus' model is simpler and is unitary in that the single genotype has similar effects upon handedness and language dominance phenotypes. The Annett model is less well-defined, principally because of the complexities of analysing the threshold for determining handedness across the mixture of normal distributions, and the model is not unified with respect to handedness and language dominance, different mechanisms seeming to relate the single genotype to the two lateralised phenotypes.

Familial sinistrality as a predictor of atypical cerebral dominance

Many studies of cerebral lateralisation routinely include measures of familial sinistrality (FS) as predictors of atypical (i.e. right-sided) cerebral language dominance (e.g., Hécaen, DeAgostini, and Monzon-Montes, 1981; McKeever, Seitz, Hoff et al., 1983; McKeever, 1986), and clinicians frequently use familial sinistrality as a guide when interpreting symptoms. This is a far less valid practice than is conventionally assumed, both because the information is unreliable, and because it does not adequately assess genotype.

For example, Bishop (1980) has pointed out that the classification of familial sinistrality is confounded with family size, since individuals from larger families are necessarily more likely to have a left-handed relative. Furthermore, Bishop (1990) has shown that, although individuals with particular genotypes are more likely to be left-handed and to have left-handed relatives, the presence of FS is of little use in predicting an individual's genotype. While Bishop has used the Annett (1985a) model for her calculations, a similar conclusion is reached using the McManus (1985a) model.

In addition, McManus (1985a, p. 21) has shown that the conditional probability of a right-hander having right-hemisphere language rises only from 4.5% to 14.8% if one parent is left-handed, and for a left-hander the probability rises only from 28.0% to 29.9%. Thus familial sinistrality has relatively little power for predicting language lateralisation. Curiously, from these figures familial sinistrality (FS) is rather more important in right-handers, and one might actually expect to find differences between groups of FS+ and FS− right-handers (cf. McKeever et al., 1983), although knowledge of FS would help very little in making predictions about a specific individual. In contrast, in left-handers differences between FS+ and FS− groups would be minimal. There certainly is no justification for the

belief that FS divides the left-handed population into those who are 'naturally' left-handed and those who are 'pathologically' left-handed (see Harris and Carlson, 1988; p. 311).

From the above it should be clear that we do not believe that information about familial sinistrality is likely to be important in defining new subgroups. Our conclusions are drawn from what we see as the best genetic models presently available, and future models may change this picture. We do not intend to suggest that information about familial sinistrality should not be collected; rather we would caution against uncritical acceptance of its effects as neuropsychologically meaningful, particularly in individual cases.

The inheritance of other behavioural and structural lateralities

Handedness and language dominance are not the only functional asymmetries of behaviour (although they are the best analysed and of most practical importance). Other lateralities, such as of hand-clasping, arm-folding, leg-crossing, and eye-dominance are to a large extent uncorrelated with handedness, and have their own separate genetic control. They are reviewed here briefly so that the reader does not confuse them with handedness per se. As with familial sinistrality, we are sceptical of the likelihood of these various lateralities telling us much about handedness, but that should not be taken to mean that such variables should not be investigated in conjunction with handedness.

Hand-clasping

When asked quickly to clasp the hands together with the fingers interlaced then most individuals characteristically place either the right thumb or the left thumb on the top; reversal to the other form is slow, difficult, and is carried out under conscious control, in distinction to the fast, automatic process for normal clasping. Left-hand clasping (i.e. the left thumb on top) is equally common in right-handers and left-handers, so that the two characteristics are statistically independent (McManus and Mascie-Taylor, 1979). Unlike handedness, there is evidence for strong geographical variation, with a strong cline across Europe and Asia, suggesting the possibility of genetic control coupled with random genetic drift (as occurs over the same range for the blood groups; Cavalli-Sforza and Bodmer, 1971; pp. 564 – 571). Genetic factors are directly implicated since left-hand clasping runs in families, albeit weakly. Genetic modelling suggests that for most populations the data are fitted adequately by two alleles analogous to (but not identical with) those invoked in the McManus model of handedness, D and C. However in Japanese populations it is necessary also to invoke a third allele S (for Sinistral), which acts as the mirror-image of D (see McManus and Mascie-Taylor, 1979). Although the model fits well, it is unusual to find stable triallelic systems, and the model also apparently violates Morgan's principle (see above). The reasons for that violation are not clear, and potentially pose problems for genetic models of hand-clasping and laterality. Nevertheless, perhaps the most important conclusion is that chance alleles resulting in fluctuating asymmetry are important in a separate, independent behavioural asymmetry.

Arm-folding

When asked to fold the arms most individuals automatically and immediately place one wrist on top of the other. Folding in the opposite direction is difficult and, like hand-clasping, is not automatic. Perhaps surprisingly, left arm-folding (i.e. left wrist on top) is largely independent both of handedness and hand-clasping (Bryden, 1989; McManus and Mascie-Taylor, 1979). Like hand-clasping, left arm-folding runs in families, also not strongly, and is modelled by a similar triallelic genetic model (although again it must be emphasised that the proposed D_a C and S alleles are at a separate locus from the hand-clasping and handedness genes, since the phenotypes are uncorrelated).

Leg crossing

When sitting in a chair most individuals consistently

cross one particular leg over the other. Blau (1946) suggests that 66% of the population puts the right leg over the left. There are few studies of leg-crossing, although the unpublished data of Michael Reiss (Dresden) suggest both that it is independent of handedness and runs in families. It is therefore possible that it is another independent asymmetry akin to hand-clasping and arm-folding.

Eye-dominance

Eye-dominance takes several forms, labelled acuity dominance, motor dominance, and sighting dominance by Porac and Coren (1976). Only sighting dominance has been studied genetically; it is typically assessed by asking a subject to use one eye for looking through a small aperture, as with a microscope; 70% of people show right eye dominance. The relationship between eye-dominance and handedness is not clear, varying between studies, perhaps reflecting co-variation between task demands (as with sighting a rifle in which right-handedness and left-eyedness, or vice versa, produces mechanical difficulties). The several family studies of eye-dominance generally show results compatible with a simple two-allele system with D and C alleles; however no formal model fitting has been carried out, in part because of uncertainties as to the relationship with handedness.

Hand-clasping, arm-folding, leg-crossing and eye-dominance are all consistent with genetic models incorporating a concept of fluctuating asymmetry, although the specific models differ in detail from those proposed for handedness. Furthermore the correlations between handedness and these other behavioural lateralities are usually so small as to be negligible. Such findings indicate that observations about left-eyedness, left arm-crossing, left hand-clasping or left leg-crossing are likely to be of no value in determining an individual's handedness genotype, nor are they likely to help in defining 'latent left-handedness' (Luria, 1970), or 'anomalous dominance' (Geschwind and Galaburda, 1987).

Handedness in animals

Handedness (or more properly, pawedness, clawedness or footedness) has been studied in a number of species, and reviewed by Annett (1967) and Walker (1980). Annett (1967) and others have argued that although individual animals show right- or left-handedness, there is no evidence for a population bias, 50% of individuals being right-handed and 50% being left-handed (as would be expected if handedness were due to fluctuating asymmetry). It is controversial whether monkeys might show a systematic population bias in handedness (see McNeilage, Studdert-Kennedy and Lindblom, 1987, for discussion with commentaries), although to us the case is far from convincing. The only species which shows convincing evidence for a non 50:50 ratio of right- to left-handedness is the parrot, although Harris's (1989) review suggests that comment far outweighs evidence.

Handedness in non-human species has been best studied by Collins in a series of papers (e.g., 1968, 1969, 1975, 1977, 1985, 1988). Collins assessed handedness in mice with a paw preference test in which food was taken from a narrow tube which could only receive a single paw; the test is repeated 50 times and the proportion of right paw entries is an index of preference. The population shows a U-shaped distribution, with some animals showing strong preferences for right or left paw usage, and others having weaker preferences. Overall almost exactly 50% prefer the right paw and 50% the left. Collins (1969) has shown convincingly, by selection experiments, that right- or left-pawedness is not under genetic control. Pawedness is however influenced by environmental factors (Collins, 1988), especially by living in a biased world in which one paw can obtain food more easily than the other, although not all animals are equally affected (Collins, 1975).

Inheritance of degree of handedness

Thus far this review of the genetics of handedness

has principally considered the genetics of the *direction* of handedness (except in so far as the Annett models consider degree of hand preference). Given the phenotypic model proposed earlier, of a bimodal distribution allowing variation in direction and degree of handedness, then *degree* of handedness might also be inherited. Few studies have examined the question, and there is some conflict with the animal studies.

Degree of handedness has been studied suprisingly little in any formal way, although McManus, Sik, Cole et al. (1988) did find that degree of handedness increased in children between the ages of 3 and 9 years, and argued that such changes were largely due to environmental factors. Recent work by Annett and Manning has suggested that degree of handedness may be associated with intelligence (Annett and Manning, 1989) and with reading ability (Annett and Manning, 1990).

Four studies have examined familial resemblance in degree of handedness; McManus (1979, 1985a) studied the parents and children and found a non-significant correlation of 0.045, whereas Bryden (1979, 1982) found a significant parent-child correlation of 0.21, and Coren and Porac (1980) found a significant correlation of about 0.10. In a three-generational study, Bryden (1987) found a parent-child correlation of 0.19, a grandparent-parent correlation of 0.32, and a grandparent-child correlation of 0.15. Together these studies suggest that perhaps 10% of variance in degree of handedness is familial (and that may of course represent shared environment rather than genes, or may be the result of shared personality factors, perhaps also under genetic control). The data do show the need for carefully distinguishing degree of handedness from direction and hand preference in family studies and in all neuropsychological studies. The frequent practice of dividing a population into 'right-handers' and 'non right-handers' (e.g., Rasmussen and Milner, 1977; Schacter, Ransil and Geschwind, 1987) completely confounds direction and degree of handedness by contrasting one group consisting entirely of strong right-handers with another containing a potpourri of weak right-handers, weak left-handers and strong left-handers.

The inheritance of degree of handedness is apparently different in animals and in humans. Collins (1985) has assessed the inheritance of degree of paw preference in mice by a selective breeding program. Animals with strong pawedness, defined as either 0 – 2 or 48 – 50 right paw entries (RPE) out of 50, or weak pawedness (10 – 40 RPEs out of 50) were selectively bred for twelve generations. There was consistent directional selection for both weak and strong pawedness (producing the so-called LO and HI strains). Although superfically suggestive of genetic control over degree of pawedness, the result conflicts with the evidence in humans of only weak genetic control over degree of handedness. McManus (1992) has argued for a separate explanation of the results found by Collins. HI and LO mice differ in several characteristics, including their sex ratio, reproductive success (miscarriage rate, litter size, etc.) and body weight (Collins, 1985). McManus (1992) has argued that these results may be due to the LO strain being more inbred than the HI strain, the differences reflecting different degrees of homozygosity (which would also influence the extent of fluctuating asymmetry; see Wayne, Modi and O'Brien, 1986). Selection might therefore have inadvertently acted on homozygosity rather than degree of pawedness, which would explain the data of Collins et al. (1985) that LO mice show more homozygosity than HI mice for the H-2 immune recognition system. An understanding of HI and LO mice is important for understanding human lateralisation, and more research is undoubtedly needed. If LO mice indeed have altered paw preference because of inbreeding, then an interesting question concerns degree of handedness in human inbred offspring (as in cousin marriages).

Handedness as a balanced polymorphism

Handedness is by definition a polymorphism (having a prevalence of the rarer phenotype of more than 1%; Cavalli-Sforza and Bodmer, 1971). Since it is under genetic control there must be forces which

maintain the stability of the two alleles. It is a basic result in population genetics that if two alleles are equally advantageous ('neutral alleles') then inevitably, after sufficient generations, one or other at random will be 'fixed' in the gene-pool and the other allele will be lost entirely, due to 'genetic drift'. That fate is avoided in balanced polymorphisms either by a high mutation rate for a disadvantageous allele (thereby avoiding its loss) or by 'heterozygote advantage', in which the heterozygote is fitter than either of the homozygotes. The classic example is sickle-cell anemia in which the deleterious effects of the homozygous form are outweighed by the heterozygote's overall advantage in conferring resistance to malaria. In a balanced polymorphism the heterozygote advantage need not necessarily be for a similar or related function to that subserved by the principle function of the gene. Thus in the case of handedness the balanced polymorphism may as well be maintained by improved running speed, a more efficient bowel, endocrine differences, resistance to coughs and sneezes or any of a host of possible pleiotropic effects, rather than some consequence of cerebral organisation or intellectual function. Ultimately all that is required is that the heterozygote has an improved reproductive success — the only real criterion of fitness. Although Annett and Manning (1989, 1990) have proposed that heterozygotes with the RS +/− genotype may be at an advantage for intelligence and reading ability, that hypothesis can ultimately only be sustained if greater reproductive success can be demonstrated.

It is very unlikely that the gene for handedness is maintained by mutation since its prevalence in the gene-pool is very high. Given the apparently constant prevalence of left-handedness (the data of Porac and Coren, 1977 are the best evidence for this over the past five millenia) then it seems reasonable that the polymorphism is balanced. At present there is no clear indication of the nature of the advantage (and here it must be said that handedness is in good company with most other polymorphisms). However a comparison of right- and left-handers in measures of fitness such as number of offspring (Table 6, based on the same data sources as Table 1a), shows a tendency for R × R parents to have more offspring than R × L parents, who have more offspring than L × L parents. However a breakdown of the data by cohorts suggests that the effect is strongest in the earlier data. However it might also be argued that earlier studies should show any such advantage better, since larger families overall allowed more scope for fitness differences to manifest. The effect is however in the opposite direction to the non-significant trend reported by McManus (1979), in the NCDS data set, for left-handed children to come from larger households. The suggestion of increased reproductive success in right-handers is also in the opposite direction to the data of Hicks and Kinsbourne (1976) in which, as McManus (1979) has reported, divorce and re-marriage were more common in left-handers. In interpreting such data it must be remembered that the theory of balanced polymorphisms applies to genotypes and not to phenotypes, and since phenotypes can come from several of the genotypes, it is not always clear that either phenotype should show an increased fitness.

TABLE 6

Mean number of offspring as a function of parental handedness, and date of birth of subjects

Year of birth	Number of studies	Parental pairs	Parental handedness		
			R × R	R × L	L × L
1880 – 1939	5	4180	3.10	2.69	2.32
1940 – 1954	5	3800	3.17	3.05	3.00
1955 – 1980	6	7323	2.49	2.60	2.57
Total	16	15303	2.84	2.72	2.56

Finding the gene for left-handedness

If handedness is under genetic control, as this Chapter argues, then in the 1990s the conclusive test of a genetic model is not construed in terms of classical genetics and ever more subtle fitting of family data, but is re-interpreted in terms of the direct examination of DNA: the proof of a genetic model consists in the finding of a DNA sequence responsible for the trait. That task is not easy even for structural and physiological abnormalities, and is especially difficult for behavioural phenotypes (see Plomin, 1990). Nevertheless we suspect that the analysis of handedness by classical genetic methods is near its limits, and that progress now depends on the techniques of molecular genetics; and only thus will differences between models be resolved.

The question therefore arises as to how to find the few thousand base-pairs responsible for handedness phenotypes in the several billion base-pairs of the human genome. McManus and Crow (1990) have argued that conventional molecular techniques may not be successful: there is no gene product in the form of a protein or mRNA; there are no karyotypic abnormalities which suggest particular genomic locations to search; and the poor penetrance of the genetic models (due to fluctuating asymmetry) means that linkage studies have little power as compared with their use in other conditions such as cystic fibrosis, colour blindness and Huntington's chorea. Unless a more general method is found for searching the genome for low penetrance genes without protein or mRNA products, then the best hope lies in serendipitous associations which point to specific hypotheses about the gene's location. A recent hypothesis may eventually help to find the gene, and it will be briefly reviewed.

Is the cerebral dominance gene in the pseudo-autosomal regions of the X and Y chromosomes?

Crow, in a series of provocative papers (e.g., 1988, 1989), has argued that the many problems surrounding the gene for schizophrenia (and in particular a paternal age effect, a season of birth effect, and atypical lateralisation) may be resolved if the schizophrenia gene is located in the pseudo-autosomal region of the X and Y chromosomes, the short region at the telomeric end of the sex chromosomes which is homologous in the two sex chromosomes and behaves genetically as an autosome (see Burgoyne, 1986). Genes in this region have obligatory meiotic crossovers in males and hence are vulnerable to mutation (which are perhaps related to paternal age) and may also be vulnerable to environmental trauma such as heat (perhaps accounting for the season of birth effect). In a provocative extension of the theory Crow suggests that the gene for schizophrenia is a mutation of the gene for handedness and cerebral lateralisation, seeing the relationship between schizophrenia gene and lateralisation gene as akin to that between the genes for sickle cell anemia and for haemoglobin.

Pseudo-autosomal genes have a characteristic signature within classical genetic data, which can be understood in terms of a dominant gene for some characteristic S. Consider an afflicted father who carries the gene S, and has genetic structure XY^S, the S gene being on the Y chromosome. He will produce sperm containing either X or Y^S, whereas the normal mother will produce ova which are all X. All their offspring will either be XY^S or XX; that his sons will manifest S and daughters will be normal. Conversely if the father had carried the gene on his X chromosome, i.e. of genotype X^SY, then his sperm will be X^S or Y, and the offspring will be XX^S or XY, i.e. his daughters will be afflicted and sons will be normal. Taken together the affected children of afflicted fathers will either be all males or all females: they will be of the same sex within families. The children of afflicted mothers show no such effect, since if of genotype XX^S she will produce X and X^S ova, and when she has children with a normal father, of genotype XY, the children will be XX, X^SX, XY or X^SY; i.e., afflicted children can be either male or female within families. The pseudo-autosomal gene manifests by showing a tendency for afflicted offspring to be of the same sex if the condition is transmitted by the father but to be equally the same or the opposite sex if transmitted

from the mother. Crow's hypothesis of a pseudo-autosomal location for the handedness gene can be tested by studying handedness within families, classified by sex of parents and offspring. McManus and Crow (1990) have calculated the expected effect size given McManus' genetic model of handedness at a pseudo-autosomal location, and have reported data on 17,034 offspring from several genetic studies. An effect is found in the expected direction, although it is not statistically significant. Power calculations suggest that despite its large size the data set is not actually large enough to provide a definitive test of the model. This problem can be attributed to the nature of fluctuating asymmetry. Whether the cerebral dominance gene is in the pseudo-autosomal region of the X chromosome must at present therefore remain an open question.

The advantages of finding the gene for handedness

In the opening paragraphs of this Chapter it was argued that the study of handedness could be paradigmatic for neuropsychology as a whole. Much of the advantage can only be reaped when the DNA responsible for the phenotype is characterised. Then a host of opportunities will arise, allowing the dissection of the clearest of all functional polymorphisms. The possible developments come in three broad areas:

(i) The application of the method of double dissociation

Double dissociation, the keystone of neuropsychological method, requires that the brains in which it is carried out are structurally and functionally similar; but that assumption may be vitiated in patients with different patterns of cerebral lateralisation (see McManus, 1987a). Accurate genotyping would allow double dissociation to be applied most conveniently to individuals of genotype DD, who will normally show the 'modal' pattern of 'left-hemisphere' tasks in the left hemisphere and 'right-hemisphere' tasks in the right hemisphere.

(ii) The ontogeny of handedness and cerebral lateralisation

Handedness and cerebral dominance are fixed fairly early in life, probably early in neural development. How the genes manifest and where may be assessed using in situ hybridisation to examine gene expression directly. The question of the gene's expression in adult life could also be resolved. An intriguing possibility, which may be resolved, is that handedness genes do not act upon cortex but instead influence basal ganglia or brainstem nuclei to cause turning tendencies, resulting in primitive preferences, which subsequently cause skill differences (a suggestion indirectly supported by the finding that children with autism show population preference asymmetry but not skill asymmetry; McManus et al., 1992). Neuropharmacological asymmetries in rodents related to turning tendencies and paw preferences (Carlson and Glick, 1989), and size asymmetries in human globus pallidus (Kooistra and Heilman, 1988) provide possible loci for genetic action.

(iii) The phylogeny of handedness and cerebral lateralisation

Animals show no obvious evidence of cerebral lateralisation of function. The gene for cerebral lateralisation must therefore have evolved within the past 3 million years or so (and Corballis (1989) argues that it is the quintessentially human gene). A dominance gene can only have mutated from a pre-existing gene, and that precursor can be identified by searching non-human genomes for genes homologous to the handedness gene. An obvious possibility, suggested by McManus (1987b), is that the lateralization gene is a mutation of the *situs inversus* gene; and if so this may allow an alternative route for identifying the handedness gene, since given the *situs inversus* gene, then the handedness gene will be a homologue of it. The mouse *iv* gene has been localised to a region of the murine chromosome 12 (Bruckner et al., 1989), and sequencing of the gene may then allow the finding of the human handedness gene. Once that route is opened then other

homologous genes, quite probably those for hand-clasping, arm-folding and eye-dominance, may be identified, and their evolutionary inter-relationships and nonhuman precursors identified.

Conclusions

The family, twin and genetic evidence cited in this review suggests that the direction of human handedness is under genetic control. Degree of hand preference may also show components which are heritable. The only successful genetic models of handedness take account of the biological constraints due to the process of fluctuating asymmetry. The model of McManus (1985a) seems marginally better able to fit the data than that of Annett (1985a,b), requiring fewer free parameters. Nevertheless, several important problems still remain unsolved, in particular sex differences, the maternal effect, and parent-offspring differences in prevalence, and we have offered our suggestions on these.

Jordan's (1911; p. 122) account of left-handedness concluded:

> "The above detailed evidence is conclusive I believe, that left-handedness is hereditary. In what way or by what principle this inheritance acts remains obscure".

We believe that the obscurity is now disappearing. The biological foundations are more secure, and the data for model fitting more extensive than for Jordan, so that the classical genetics are now as well established as is practical given the constraints of sample size and statistical power; and those data and models certainly suggest a hereditary basis for handedness. The new genetics founded in molecular biology should now allow the understanding and development of what Jordan called "the promise revealed" (p. 123).

Acknowledgements

Preparation of this Chapter was aided by a research grant from the Natural Sciences and Engineering Research Council of Canada to M.P.B. M.P.B. was supported by a Killam Research Fellowship from Canada Council. The authors thank Susan Gagné and Paul Brown at the University of Waterloo for their assistance in compiling the tables and the bibliography.

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VOLUME 6

1992

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