CHAPTER 7: A GENETIC MODEL OF HANDEDNESS

"the determinant for the distribution of
right and left in the animal kingdom is
what we generally call chance"

Ludwig (1932) cited in Fritsch (1968, p 103)

7:1 The requirements of a model of handedness

Any model of handedness has to meet certain minimal requirements.

i) It must account for the data in the literature showing a familial trend in handedness. Left-handers represent about 10% of the children of two right-handed parents; 20-25% of the children of one right and one left-handed parent; and about 40% of the children of two left-handed parents. (see Table 7.1 for further details).

ii) It must explain the relatively high proportion of monozygotic twin pairs which are discordant for handedness (that is, in which one is right-handed and the other is left-handed).

iii) It should account economically for the phenomenon of cerebral speech dominance, which is partially correlated with handedness; thus using dichotic listening tests, unilateral ECT or the sodium amytal test, about 10% of right-handers and about 35% of left-handers show right hemisphere speech dominance. It should also account for the discrepancy between the incidence of crossed speech dominance in right-handers as assessed by dichotic tests (about 10%) and that assessed from clinical studies of aphasia (about 1-3% at maximum).

iv) The model should be compatible with the known inheritance of other biological asymmetries e.g. <u>situs</u> (the laterality of the viscera), and possibly also hand-clasping and arm-folding (see Chapter 9 for an account).

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

In this and the following chapter I wish to present a two-allele, single-locus model, with complete penetrance in the homozygotes, and 'additivity' of the heterozygote; this model I will suggest, can satisfy all of the above requirements.

Before starting to fit a model to the handedness data it is necessary to clarify several points.

It is not possible to fit a genetic model unless the phenotypes are clearly known. Earlier, in Chapter 2, I have discussed the phenotypic description of handedness at some length and have concluded that there are, at least for genetic purposes, exactly two types of handedness, right and left, and that the best criterion for determining to which of the two categories an individual belongs, is the hand used for writing. In adopting such a position I am in complete disagreement with the position of Annett (e.g.

1976, "Hand preferences vary not discretely but continuously"); this inevitably conditions the nature of our respective genetic models, since, of necessity, hypothesised genotypes are closely dependent upon supposed phenotypes.

I am probably in disagreement with a large number of authors in that I feel that pathological left-handedness (and of course, by symmetry, pathological right-handedness), are either very rare, or possibly even non-existent. Certainly I do not feel that left-handedness can be regarded as secondary to birth trauma or birth stress (as does for instance Bakan, 1978), and in Chapter 3 I have given extensive empirical evidence for this position. But neither do I feel that pathological left-handedness occurs in any other form; my evidence for this position has been presented in the previous chapter.

I take such an apparently iconoclastic position on these issues since I feel that thus the solution to the problem of the origin of left-handedness is rendered less obscure.

7:2 The biological background

In discussing the biology of asymmetry we must clearly distinguish fluctuating asymmetry from directional asymmetry.

7:2.1 Fluctuating asymmetry

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

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

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

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

7:2.2 Directional asymmetry

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

Directional asymmetry is biologically very different from fluctuating asymmetry. That it is of greater importance is suggested by the fact that in its extreme forms we do not even question its occurrence. Why the heart is on the left is neither a simple not a trivial

question. If the heart were on the left in 50% of cases then the answer might be simple - that fluctuating asymmetry followed by canalisation inevitably produced it that way. To use a physical metaphor, to maintain an asymmetry we must search for a stabilising force, for otherwise the system would inevitably return to symmetry; or rather, a directional asymmetry will return to a fluctuating asymmetry.

Whilst directional asymmetry can (and one might argue, must) have some form of genetic control, there is an important limitation upon such control. Morgan (1976) has argued that it is, in principle, unlikely that a gene carries direct information about chirality; that is, paired alleles have not been shown, in any convincing case, to produce enantiomorphic phenotypes in their carriers. Thus, if one homozygote of an allelic pair produces one particular directional asymmetry, then the other homozygote cannot produce the mirror-image directional asymmetry. (An apparent exception to this rule is discussed in detail in Chapter 9). The present model relies heavily upon Morgan's principle for its origins, although not, of course, for its justification as a satisfactory fit to the data.

The need for a new model of the genetic control of handedness is two-fold. First I will argue that no previous model adequately fits the available data. Second, I will suggest that all previous models (with the single exception

of Annett, 1978) have not satisfied Morgan's principle, since they have alleles which are symmetric in their effects. As a result I will argue that any adequate model of the inheritance of asymmetry must itself be inherently asymmetric. This principle may be satisfied in the case of handedness by allowing one homozygote from an allelic pair to produce a directional asymmetry, and the other homogygote to 'produce' a fluctuating asymmetry; that is, the latter genotype has no control over the asymmetry and hence it is, in effect, a null gene.

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

In most vertebrates the heart and stomach are on the left and the liver is on the right. This situation (situs solitus), (SS), is occasionally mirror-reversed to give situs inversus, (SI). Spemann and Falkenberg (1919) found that tying a fine thread around the mid-line of a developing newt embryo produced conjoined twins. The left-hand member of the pair almost always showed SS, whilst the right-hand member showed SI in about half of the cases. A similar situation exists if the embryo is completely split in two (Ruud and Spemann, 1923). Analogous findings have been reported in conjoined trout (Lynn, 1946) and conjoined human twins (Newman, 1940). In other animals SI has been shown to be produced teratogenically (Shehenfelt, 1974), by cold (Newman, 1925)m or by irradiation

(Wilson et al, 1953), but in no case does the incidence rise above 50%

The iv mutation in the mouse, when homozygous, produces SI in exactly 50% of cases (Layton, 1976). Nevertheless the iv gene shows complete penetrance. When two iv homozygotes are mated then the progeny show 50% of SI, irrespective of the particular phenotype of the parents. A similar situation exists in another mouse mutation (Tihen et al, 1948) producing SI, and also in the platyfish Xiphorus maculatus (Baker-Cohen, 1961). In man, Kartagener's syndrome, of chronic sinusitis, bronchiectasis and situs inversus, is inherited as an autosomal recessive, with the limitation that only 50% of homozygotes show the SI component of the syndrome (Afzelius, 1976). Amongst human monozygotic twins showing situs inversus, 46% of 13 reported pairs are concordant, the rest discordant (Lowe and McKeown, 1953); the expected values are 33.3% concordant and 66.6% discordant.

Directional and fluctuating asymmetry can also be seen in the arrangement of the optic chiasma in the flatfish, the Heterosomata (see Chapter 9 for further discussion).

A behavioural example of fluctuating asymmetry is that of Collins (1970), who looked at the pawedness of mice which had been inbred for 28 generations (and hence we may assume were almost certainly homozygous at all loci).

Of these animals 50% were left-pawed and 50% were right-pawed, with no evidence of any inheritance over a further three generations (Collins, 1970).

7:3 The data to be explained

7:3.1 Familial data

The literature contains seven studies of the incidence of left-handedness in the progeny of R x R, R x L and L x L matings (Ramaley, 1913; Chamberlain, 1928; Rife, 1940; Hubbard, 1971; Annett, 1973; Ferranato, 1974; and Annett, 1978). In using these data sets certain modifications have been made. The data of Chamberlain (1928) have been used as quoted by Annett (1973), not withstanding the trivial inconsistencies demonstrated by Levy, 1976. In using the Chamberlain data I have considered only those individuals obtained by random sampling since the incidence of left-handedness is higher amongst those families obtained by special appeal (Chi-squared = 3.43, 1 df, $p < 0.10$), and thus one suspects a response bias. Similar considerations for the data of Annett (1973) mean that only the randomly obtained data have been included. For the data of Hubbard (1971) it has been assumed that all of those progeny with one left-handed parent have only one left-handed parent; on the basis of random assortative mating one would have expected only four individuals to have come from L x L matings. Whilst I would also have liked to use the data of

Falek (1959), this was not possible due to the sample not being complete, and there being no indication of the overall incidence of left-handedness in the propositus generation.

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

I have also used 5 distinct sets of data obtained from two large-scale surveys of my own. The data of survey 1 were obtained by questionnaire given to undergraduates at the University of Cambridge in May 1977; the students were asked to provide information on their own handedness and on the handedness of their siblings,

parents and grand-parents (it was stressed to them that it was preferable to not reply to a question rather than to guess at an answer). Left-handedness was classified on the basis of writing hand, with the single exception that those right-handed writers who originally wrote with their left-hand, but had been forced to write with their right hand,were classified as left-handed. Two sets of family data were obtained from this study; first, the students' and students' siblings handedness as a function of parental handedness (ICM-1 propositus generation); and second, the parents' handedness as a function of the grand-parental handedness (ICM-1 parental generation). The response rate to the questionnaire was difficult to assess accurately but was of the order of 50%. The second study, survey 2, was carried out in June 1977, and the questionnaire was given to all Cambridge graduates who were collecting their degrees in person. The questionnaires were distributed on the eve of the graduation ceremony. Information was thus obtained not only from the students, but also from other members of the students' family, so that fairly accurate information could be obtained on the handedness of parents, parents' siblings, the grand-parents, and the great-grand-parents, as well as on the students' siblings. Once more it was emphasised that questions should be answered only if the answer was fairly certain, guessing being discouraged. Handedness was classified as in the previous study. From this study three separate sets of family data could be obtained; students and students's siblings as a

function of parental handedness (ICM-2 propositus generation); parental and parental siblings' handedness as a function of grand-parental handedness (ICM-2 parental generation); and grand-parental handedness as a function of great-grand-parental handedness (ICM-2 grand-parental generation). The response rate of this study was of the order of 20%. Other aspects of these questionnaires have been discussed in some detail in Chapter 2.

The data from all these studies are collected together in table 7.1 The data from L x L matings are relatively restricted, and, except in the case of Chamberlain (1928), I have lumped together data from separate studies with broadly similar overall incidences of left-handedness in the progeny.

Figure 7.1 shows the data of Table 7.1 plotted graphically, with the proportions of left-handed progeny of the three mating types shown as a function of the overall incidence of left-handedness amongst the progeny. Note that when this is done it is clear that there is a fairly clear relationship between the data from all of the studies.

That there are differences in incidence of left-handedness in the progeny of various studies is clear from Figure 7.1. These differences are far too large to be simply a function of sampling errors. The differences are

far too large to be simply a function of sampling errors. The differences are compounded in their complexity, by differences in incidence of left-handedness in the parental generations of different studies, even when the effect of progeny variation is partialled out.

These differences in incidence represent a major problem for any model of left-handedness. One can hardly make the usual assumption of classical genetics, that all differences in incidence are due to differences in allele frequencies, since it is clear that by using different definitions of left-handedness, the same study may be used to produce different progeny incidences of left-handedness. Clearly in such a case it would be absurd to argue that the allele frequencies had also changed. There are two approaches to the problem. We may follow Nagylaki and Levy (1972) and Levy (1976) who argue that data are invalid for genetic analysis unless the parental incidence of sinistrality is equal to the progeny incidence of sinistrality. That process of exclusion left them with only a single set of data, that of Rife (1940). They still however, make the assumption that Rife's criterion is the correct one; if one cared to dispute Rife's definition of handedness one would be left with absolutely no data at all with which to test a model. This position seems somewhat unsatisfactory. The alternative position, adopted by Annett (1978), seems far more realistic, In the first instance one assumes that all studies have the same allelic proportions, and hence

have the same proportions of the true phenotypes (i.e. in her case, RS+ and RS-). Differences in apparent proportions of sinistrality are then due to differences in criterion or threshold of left-handedness. As she points out (Annett, 1978), this has a close similarity to the methodology of signal detection theory where, despite differences in response bias (Beta), one is trying to find a true sensitivity (d'). In the following analysis I shall follow Annett in attempting to make corrections for differences in incidence of left-handedness, and thus will attempt to fit all of the available data, warts and all. My actual calculations for these corrections will however be somewhat different to those of Annett.

Appendix A7:3 discusses the possibility of assortative mating for handedness, and concludes that it is of little or no consequence.

7:3.2 Twin data

There are eighteen different sets of twin data in the literature; these are summarised in Table 7.2.

Several claims have been made about handedness in twins:-

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

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

iii. that twins in general have a higher incidence of sinistrality than do singletons.

In Chapter 4 I have critically reviewed evidence for these statements and find none of them adequately supported by the data. This is important, since on the basis of (ii) and (iii) in particular, Nagylaki and Levy (1973) have argued that twins are not suitable for fitting to genetic models, since twins show increased pathological left-handedness, and also, in MZ twins, "ectodermal mirror-imaging". Since there is no evidence for ii and iii, genetic models should be able to cope with data from twins as well as that from singletons. In particular, as Corballis and Beale (1976) have pointed out, the model of Levy and Nagylaki cannot cope with the MZ twin data at all.

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

7:4 Previous models of handedness

It is instructive to compare previous models of handedness; for convenience the essential genetics of each are summarised in Table 7.3.

Ramaley (1913), not long after the re-discovery of Mendel's laws, proposed that there were two alleles which we may label L and R. L was recessive and there was complete penetrance. Thus all LL individuals were left-handed, whilst all RR and RL individuals were right-handed. As Ramalay himself recognised this model fails since it predicts that all of the children of two left-handers should themselves be left-handed; even a single exception, such as he reported, and as were later reported by Jordan (1914), disproves the hypothesis. Rife (1950) proposed a modified form of the Ramaley model. Not only were LL genotypes left-handed, but so also were a proportion of the heterozygotes. This model thus allows that neither right nor left-handers breed perfectly true, since the left-handers' genepool now contains R alleles, and vice-versa. Trankell (1955) produced a model which was also a variant of Ramaley's model, In Trankell's model it is the LL genotypes rather than the heterozygotes which show partial penetrance, and hence allow L x L matings not to breed true. Whilst both are improvements upon Ramaley's model, neither that of Trankell nor that of Rife will adequately fit all of the requirements. although as will be seen below, the Trankell

model can be made to fit quite closely.

Annett (1964) proposed yet another variant upon the Ramaley theme. Annett complicated the problem by arguing not that penetrances in the Ramaley model were wrong, but that the phenotypic classification was itself in error. Thus she proposed that the heterozygotes produced a separate and distinct phenotype known as 'mixed' handedness. This model clearly fails since both R x R and L x L (as opposed to M x M etc.) matings should breed true, and yet the data of Annett (1972) clearly shows that this is not the case. The logic of increasing the number of phenotypes is also somewhat worrying since it inevitably means that all previous data sets in the literature are inadequate for testing the model.

Levy and Nagylaki (1972) proposed a yet more complex model. They argued that it was necessary to postulate four alleles, two at each of two loci, the two loci segregating independently. There are thus nine genotypes. They also postulated yet another increase in the number of phenotypes, arguing that as well as individuals whose writing hand was the right or the left, each group could be sub-divided into two further groups according to whether cerebral control of the hand was ipsilateral or contralateral. The possibility of ipsilateral hand control, whilst intriguing, seems not to be supported by either anatomical or clinical evidence. That not all pyramidal fibres decussate in the medulla is

well accepted; and it seems probable that in a few cases no decussation takes place at all at the medullary pyramid. But this does not demonstrate that control of the hand is ipsilateral, since the fibres might well decussate at other levels. The critical observation, which receives no adequate support from the literature, is whether individuals occur in whom after a cerebral lesion there is ipsilateral loss of motor control

The most serious criticism however of the Levy and Nagylaki model is that it simply fails to fit the data adequately. Hudson (1975) has pointed out the model's failure to account for the data of Annett (1972) or Chamberlain (1928). More seriously still, as Corballis and Beale (1976) have pointed out, the model can in no way account for the twin data, since it makes no allowance for monozygotic discordance of handedness.

The most recent model of handedness is that of Annett (1978). This model was first postulated in 1972, but only in 1978 were the actual genetic mechanisms stated. The model is completely different to any of the others described. Its most important aspects are that it is compatible with Morgan's principle, and that it can account for different manifest incidences of left-handedness in different studies. It also makes predictions about clinical data on aphasia and speech dominance (Annett, 1975, 1976), although these predictions are rather less powerful when it is realised that

in the later paper these data are themselves used to define the parameters of the model.

Annett's model proposes that there are two phenotypes, RS+ and RS-. RS- individuals are normally distributed with mean 0.0 and variance of 1. RS+ individuals have a normal distribution, but are shifted to the right and have a mean of z, with a variance of 1. A threshold, x, differentiates right-handers from left-handers. Annett (1978) shows that the model is capable of dealing with all the family data, and indeed my calculations show that this is so for all of the 14 studies of Table 7.1 (see Figures 7.2 and 7.13). The great defect of the model is that in order to account for the twin data, Annett has to postulate that the RS+ distribution has a different mean to that in the singleton model. In other words, the model proposes that the inheritance of handedness is different in singletons and in twins, This is a serious objection, and certainly from my calculations there is no possible single pair of values of z and the proportion of RS- individuals, which will adequately fit all of the data of table 7.1 and of table 7.2,no values being acceptable at better than the one in a million probability level. Annett's error, I would argue, is not in the form of the model - that is correct, and I would argue that in some sense the model I wish to propose is a special case of the Annett model - but in her description of the phenotypes. By allowing handedness to be a continuous rather than a discrete variable, her model becomes

distorted, and hence fails. And of course the repeated fitting of yet more family data alone, as in Annett (1979), will never convince one of the overall adequacy of the model.

In summary, most of the previous models of handedness have failed as they do not satisfy Morgan's principle. The sole exception is the model of Annett (1978), which I would suggest fails due to its insistence upon an unrealistic phenotypic conception of handedness.

7:5 The Model

As stated earlier, the present model is explicitly based upon the information described in 'The Biological Background' (section 7:2 above). It is proposed that there are two alleles, D and C. Allele D (for Dextral), produces 100% right-handers when it is homozygous. Allele C (for Chance), 'produces', in its homozygous form, pure fluctuating asymmetry (i.e. there is no control over the phenotypes of the progeny). Thus exactly 50% of the CC genotype are right-handed, and 50% are left-handed. Note that in this case, 50% is not an arbitrary figure (45% or 23%, for example, could not be fitted to the same argument), but is a precise statement of a particular genetic manifestation. Also it must be emphasised that although only 50% of CC individuals are left-handed, this does not mean that the CC genotype is only partially penetrant. It shows 100% penetrance

for its real phenotyoes, which is fluctuating asymmetry, and hence, as a secondary consequence, produces only 50% of left-handers.

Thus far the model can be defined a priori from a knowledge of the biology of asymmetry. The next step is less predictable. The problem is that the proportion of left-handers to be expected from the heterozygote, DC, is undefined. If C is recessive (i.e. the heterozygote manifests as the commoner of the two homozygotes) then one would expect 100% right-handers from the DC genotype. Conversely if C is dominant (i.e. the heterozygote acts as the less common of the two homozygotes) then one would expect 50% of left-handers from the heterozygote. But of course there could also be an infinity of intermediate positions in which the heterozygote produces a proportion, x, of left-handers, where x is between 0 and 0.5. In particular I wish to call the position exactly intermediate between the two extremes, 'additive'. The additive DC genotype thus produces 25% left-handers and 75% right-handers. Whatever the particular value of $p(L|DC)$, the use of values other than 0 or 100 may be seen as examples of the 'random phenotype concept' (Birnbaum, 1972).

The models to be discussed are thus a restricted set of those to be called model I in Chapter 9.

Genotype	p(left-hander)	p(right-hander)
DD	0.0	1.0
DC	x/2	1.0 - x/2
CC	0.5	0.5

The parameter x controls the degree of dominance of the heterozygote. Thus if x = 1, then C is recessive, if x = 0 then C is dominant, and if x = 0.5, then C is 'additive'.

Thus far it is a relatively simple matter to choose a particular value of x (thereby defining the genetics entirely), and to predict the proportions of left-handers which would result from particular parental pairs, or in particular twin-types (for details of the calculations see the Appendix). The major problem is to fit the models when the apparent incidence of left-handedness is different in different studies, and one has no idea which, if indeed any, of the values is actually correct. To solve this problem it is necessary to define two incidences of handedness. Let $p(L_m)$ be the manifest proportion of left-handers in a particular population; thus $p(L_m)$ can vary between populations, or even within a population if the criterion for left-handedness should be changed.

By contrast, let $p(L_t)$ be the true incidence of left-handedness, which I would propose, at least in the first instance, is constant in all the different populations being studied. Clearly, whilst $p(L_m)$ can be directly estimated

from the data, the value of $p(L_t)$ may only be hypothesised. In reality, the process of calculation is to hypothesise particular values of x and $p(L_t)$, and then to find the fit of that particular model. The calculation then proceeds combinatorially, for all possible values of x and $p(L_t)$ in the desired range, finding all of those which fit adequately.

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

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

ii. There may be a response bias, whereby left-handers tend not to respond to questionnaires (as perhaps may have been true at the turn of the century) or they tend to over-respond to questionnaires (as may well be true now). And of course separate corrections must be made for both the parental and propositus generations, $p(L_t)$ for parents, being assumed to be equal to $p(L_t)$ for the progeny.

Scrutiny of the origins of the data presented in Table 7.1 suggests that in all parental cases, and almost all of the progeny cases, criterion shifts cannot be eliminated. But similarly in most surveys, response biasses cannot be eliminated either. Exceptions are my own surveys, in which I am forced to argue that the correct criterion of left-handedness has been used, and the study of Mascie-Taylor, who I would also argue has used the correct criterion, and in which study there was probably no response bias since there was almost one hundred percent ascertainment; it is noteworthy that in that study the parental and progeny incidences are equal, and the incidence of sinistrality is very close to that which I will later hypothesise. In Appendix 7:2 I give details of the calculations using both methods, and suggest that in most cases they give sufficiently similar results to mean that they are, for most practicable purposes, indiscriminable. I have therefore, for simplicity, assumed that all differences in incidence of $p(L_m)$ are due to criterion shifts alone.

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

a. some true right-handers are manifesting as left-handers, and
b. some true left-handers are manifesting as right-handers.

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

Making these assumptions it is possible to fit the data of Tables 7.1 and 7.2 to a whole series of models, and to find which are compatible with the data. The details of all calculations are given in Appendix 7.2

7:6 Fitting the model

Fitting the model of handedness requires estimation of two parameters, x, the degree of dominance (i.e. $p(L|DC)$), and $p(L_t)$, the true indidence of left-handedness. This fitting has been carried out by predicting the expected results for particular values of $p(L_t)$, and x, and then testing the goodness of fit by means of a Chi-squared test. This is carried out for all possible values of x in the range 0(0.05)1.0, and $p(L_t)$ in the range 0.05(0.005)0.25; values of $p(L_t)$ have been used outside of this range, but they do not give interesting results (there being no fit at all), and they will not be considered here. Details of the method of goodness of fit testing are given in Appendix 7:1.

Before fitting a new model it is necessary to confirm that none of the old models is capable of fitting the data when the new corrections are made for differences in the incidence of handedness. Figure 7.3 shows the goodness of fit of the Rife model, that is a model in which $p(L|RR) = 0.0$, $p(L|LL)=1.0$, and $p(L|RL) = x$, where x is in the range of 0.0 to 1.0. A special case of this model, when $p(L|RL) = 0.0$, is the Ramaley model. Figure 7.3 shows that particular values of x, and the true incidence of left-handedness will adequately fit either the twin data, or the family data, but that there is no overlap at all of the distributions, and indeed all Chi-squared values for the combined data are massively significant, the lowest being, for $p(L_t) = 0.25$, and $p(L|RL) = 0.4$, equal to 194.5, with 66 degrees of freedom (liberal estimate of df, see appendix 7:1).

Figure 7.4 shows the rather different result for the Trankell model, in which $p(L|RR) = 0.0$, $p(L|RL) = 0.0$, and $p(L|LL)$ can vary in the range from 0.0 to 1.0. As with the Rife model, when $p(L|LL) = 1.0$, this is also the Ramaley model. Once more there are adequate fits for both the twin data and the family data considered on their own; this time there are also adequate fits for the combined data, the best fit being with $p(L_t) = 0.075$ and $p(L|LL) = 0.30$ (Figure 7.5). Despite, therefore, the original reservations about the theoretical inappropriateness of the Trankell model, it is capable of fitting the available data adequately; this point will be returned to

later in a more general discussion of my own model, and of the models in general.

We may now fit the data to the new model.

Figures 7.6a, 7.6b and 7.6c show the goodness of fit of various forms of the model to the data from R x R, R x L and L x L matings. It can be seen that the R x R data discriminates little between models, the R x L data discriminates well, and that the L x L data also discriminates moderately well (although [redacted] inevitably hampered by small sample sizes). The goodness of fit of the combined family data is shown in Figure 7.6d. A whole range of models will fit this data, from dominant through to recessive, with different values of $p(L_t)$ for particular models.

Figures 7.6e and 7.6f show the goodness of fit of the data from MZ and DZ twins. Whilst DZ twins appear to discriminate very little between models, they clearly exclude the a priori probable models, i.e. the recessive and dominant. The MZ twins show a far greater selectivity. Combining the results of the family studies, and the MZ and DZ twins, we obtain the distribution of Figure 7.7. It can be seen that there is now a relatively small area which can account for all of the data. The minimum Chi-squared value of 70.6 is found at values of $p(L_t)$ of 0.080. and degree of dominance 0.25 (that is the hetero-

zygote produces 12.5% left-handers). However there are several other pairs of values which produce almost equally good fits. In particular I would like to emphasise those models in which the degree of dominance is 0.5 (that is, that the heterozygote produces 25% left-handers, exactly mid-way between the two homozygotes). I will call this model additive, after the usage adopted in polygenic models, although the analogy is not exact, since in polygenic systems it is the <u>individual</u> phenotype which is mid-way between extremes, whereas in the present case it is the <u>population</u> phenotype which is mid-way between the homozygotes. One advantage of the additive model is that as will be shown in Chapter 9, models to be fitted to hand-clasping and arm-folding data also have to have similar 'additive' genes, and that at least one such pair is necessary.

Considering the additive models, the miniumm Chi-squared value is 79.4, at a $p(L_t)$ of 9.0%: however, at $p(L_t)$ of 9.5% the Chi-squared value is only 79.5. For reasons which will becomeapparent later, I have chosen to concentrate upon this latter value.

Tables 7.1 and 7.2 show, as well as the raw data for families and twins, the predictions of these two particular versions of the model (i.e. $p(L_t)$ and degree of dominance of 8.0% and 9.5%, and 0.25 and 0.5 respectively). Scrutiny of this table shows several features. First, the two models

often show only minimal differences in their predictions, thus making discrimination very difficult. Second, the overall Chi-squared values are heavily dependent upon just a very few datasets. In particular the data of Hubbard (1971), and my own study (ICM-2-grandparents) account for much of the Chi-squared in the family data. The Hubbard study was difficult to fit as R x L and L x L data had been lumped together; my own grand-parental study had a high a priori probability of being in error since it was assessing the handedness of the propositus' grand-parents as a function of the propositus' great-grand-parents. Amongst the twin studies, the data of Loehlin and Nichols (1976) seems to fit badly for both MZ and DZ twins. This study was the only twin study to be conducted by means of a postal questionnaire, and thus might be less reliable than the others.

When these aberrant values are excluded, one obtains Chi-squared values of 51.21, with 60 df for the 'a' model, and 46.58, with 60 df for the 'b' model, both values being highly acceptable in statistical terms. These values are also acceptable if one uses a more conservative estimate of the number of degrees of freedom, i.e. 48.

The fit of this slightly reduced data set (i.e. with only 12 sets of family data, and 17 MZ and 16 DZ twin data sets), isshown in Figures 7.8 and 7.9 for my own model, Figure 7.10 for the Rife model, Figures 7.11 and 7.12 for the

Trankell model, and Figure 7.13 for the Annett model. Clearly all of these models might be expected to show some improved fitting to the more homogeneous data sets.

My own model now shows a better fit over a slightly wider range. The Rife model also shows a slightly better fit, but there is still not even a hint of a combined twin and family fit. The Trankell model shows a somewhat improved fit for both family and twin data. The Annett model, like the Rife model, shows better family and twin fits, but still there is no combined fit even at the one in a million level.

In summary, by making assumptions about the nature of the differences in incidence of handedness in different studies, and by using a genetic model in which fluctuating asymmetry plays a large part, it is possible to fit all of the existing data using a single model, and a single prediction of the incidence of $p(L_t)$.

7:7 Discussion

It is still however necessary to consider the fact that the Trankell model seems to fit the data. We may consider both my own model and also the Trankell model (and indeed many other models as well), as mathematical (although not biological) variants of a general model in which $p(L|DD)$ may vary between 0.0 and 1.0, and $p(L|DC)$ and $p(L|CC)$ may also

vary between 0.0 and 1.0. As well as this, of course the value of $p(L_t)$ may also vary to fit the model; the result is a vast array of possibilities. If we allow there to be 21 discrete value of each of the conditional probabilities, and there to be 41 discrete values of $p(L_t)$, then a total of 379701 models can be formed; of course a large number of these models are not possible on logical or mathematical grounds. Nevertheless it should be clear that there is a high probability that models with apparently very different theoretical bases, may well have remarkably similar predictions for the range of situations we are considering here,(although this of course is not to say that they must <u>always</u> be the same). It is also necessary to remember ~~that~~, as Morgan has pointed out, that if one has enough free parameters in a model then of course it may be made to fit almost any data; in this respect my own model, and that of Tranke l, are both superior to the 'general' model in that they both specify clearly in advance two of the four parameters. I would however, like to suggest that there are other reasons for taking more notice of these two models, and indeed in particular of my own one model. At the very beginning of this paper I stressed that there were two further requirements of a model; it must be biologically convincing; and it must give some account of the data from studies of cerebral speech dominance. I would like to argue that the Trankell model is not biologically convincing, since there are good <u>a priori</u> reasons for favouring a model which contains

fluctuating asymmetry.

That my own model is precise in its predictions may be shown by a set of tables. Table 7.4 shows the expected proportions of the three genotypes in individuals of particular handedness and of particular parental types, for a model in which $p(L_t) = 9.5\%$, the inheritance is additive, and it is assumed that manifest incidence is equal to true incidence. The figures are given to 8 significant places to assist any further calculations from the table. Table 7.5 shows the expected proportions of MZ twin pairs by parental handedness, and Table 7.6 shows the probability of MZ twins being of a particular genotype, given their own twin pair-type, and the parental handedness. These data will be used further in the next chapter.

If the present model of handedness is correct then it allows a re-interpretation of the several sets of data in the literature associating left-handedness with mental deficiency (see chapter 6:6.4). These data sets have often been interpreted as evidence that left-handers in general are of lower intelligence, as if the handedness were somehow the <u>cause</u> of the mental deficiency. An alternative view is that a prior severe brain insult, e.g. due to trauma, metabolic or chromosomal abnormality, may have caused the low intelligence, and also have caused a massive amount of 'biological noise' which has over-ridden any pre-existing directional asymmetry, to produce

fluctuating asymmetry, and hence left-handedness in up to 50% of cases. If true then one might also predict that any other developmental abnormality of the brain might also produce a local increase in biological noise, and hence fluctuating asymmetry, and 'phenocopy left-handers'. One possible example of this is in congenital partial or total agenesis of the corpus collosum. The condition is associated with normal intelligence, and is often detected only at routine post-mortem, or as an incidental finding on ventriculography or computerised tomography. Nevertheless a review of the few cases in the literature for whom the handedness is given, shows that of the 19 cases, 9 (47.5%) were described as left-handed (Bossy, 1972; Dennis, 1976; Ettlinger et al, 1972; Ferris and Dorsen, 1975; Field et al, 19 Gardner et al / 1975; Sadowsky and Reeves, 1975). Although this is a small sample, it is tempting to conclude that the incidence of left-handedness in callosal agenesis is indeed raised, as might be predicted from the theory.

As yet no account has been given of why the heterozygote in my own model should be exactly intermediate between the two homozygotes in its expression. Three possible mechanisms can be suggested:-

i. If the D allele produces a buffering substance, and the C allele a disrupting substance, then genotype DD will produce only buffer, and genotype CC will produce only disruptor, thereby resulting in either directional or

fluctuating asymmetry respectively. The heterozygote, DC, would produce both substances, and the particular effect of this would be dependent upon the dose-response curves of the two substances, and might possibly result in an effect midway between the two homozygotes.

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

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

APPENDIX A7:1: TESTING THE STATISTICAL SIGNIFICANCE OF FIT

Whilst it is a relatively simple task to calculate Chi-squared values for the goodness of fit of particular models, it is necessary to test the significance of such fits. To do this requires knowledge of the necessary number of degrees of freedom. For the twin data this seems fairly simple, one degree of freedom being used to test the fit of the theory to a 3 x 1 matrix (i.e. n(R-R), n(R-L) and n(L-L)). One degree of freedom is used since there are a total of three cells in the matrix, thus setting an upper bound of three degrees of freedom. But one of these degrees of freedom is consumed since it is necessary to know the total sample size (i.e. N), and a further degree of freedom is used since one needs to know the overall incidence of left-handedness (i.e. $p(L_m)$). This leaves a single degree of freedom; and here my calculations agree with those of Annett (1978), who also uses one degree of freedom for fitting twin data.

Fitting the 3 x 2 matrix of family data is not so simple. Classically one would argue that a 3 x 2 table has (3-1) x (2-1) = 2 degrees of freedom; and indeed it would do so if one were testing simple homogeneity of the table with respect to its edge totals. Certainly this argument gives us a conservative lower bound for the degrees of freedom of two. However the table is not strictly a 3 x 2

but is instead 3 tables each of size 2 x 1. It would be quite possible to carry out a survey in which firstly one randomly ascertained the manifest incidences of left-handedness in the separate generations, and then looked for, say, just children of one right and one left-handed parent. One could then predict the expected percentage of left-handed progeny and see how this compared with the observed value, using a Chi-squared with one degree of freedom to test the result. This indeed is what, in effect, I have done in the R x R, etc, sections of Figures 7.2 - 7.13. Since there are three separate tables it seems illogical to have only two degrees of freedom for the combined table. Consider the hypothetical study above in which I ascertained the progeny of only R x L matings. From this I obtain a value of Chi-squared, say X (R-L), with one df. I later look at the same population again and examine just R x R matings, and then obtain a Chi-squared value of X(R-R), also with one degree of freedom. The combined result thus has two degrees of freedom. If now I finally ascertain the L x L matings, I obtain a third value of Chi-squared, X(L-L). If I were now to have to test the combined result of all three studies with only two degrees of freedom, I would be in an awkward position. Let the probability of obtaining the result from the first two combined studies (with a Chi-squared value of X(1,2)), be p(1,2). Then by adding the third study, I produce X(1,2,3), where X(1,2,3) = X(1,2) + X(L-L). And X(1,2,3) has a probability p(1,2,3). But since X(L-L) can only be equal to or greater

than zero, and in all probability, X(L-L) will be greater than zero, it is necessarily true that $p(1,2,3) > p(1,2)$. Thus in obtaining further data I am merely disadvantaging the theory, since by using X(1,2,3) there is necessarily a greater probability of rejecting the theory than by using X(1,2). This seems an absurdity, an absurdity which is readily removed by testing X(1,2,3) with three degrees of freedom.

I would therefore argue, on logical rather than statistical grounds, that one must use three degrees of freedom for fitting the sort of data I have described. In so stating I am disagreeing implicitly with Annett (1978), who uses two degrees of freedom, but does not justify her actions in so doing. Ultimately the best way of resolving this dispute is probably by some form of Monte Carlo simulation, and finding whether two or three degrees of freedom fits the observed values better. In the graphs shown earlier in this paper I have given in general the results for a 'conservative' test (i.e. with 2 dfs), but have also indicated the 5% limits for a more liberal test with three degrees of freedom.

A further statistical problem concerns low expected values in the Chi-squared calculations. Most textbooks stat that expected values must be greater than 5; a few state that 3 is an acceptable lower limit. Most calculations are however looking for significant heterogeneity, where as in t

present study I am primarily concerned with the goodness of fit of predictions to data. Since low expected values can only produce spuriously high values of Chi-squared (and thus produce falsely significant results), I have used a minimum acceptable expected value of 1.5; in so doing I may have only rejected some models erroneously, I am unlikely to have accepted any by mistake. The utility of such an approach is that it allows one to fit data from relatively small studies without having to combine otherwise disparate studies.

APPENDIX A7:2 THE CALCULATIONS

Consider a system with two alleles at a single locus, and hence three possible genotypes, G(1), G(2) and G(3). There are two possible phenotypes from these three genotypes, P(1) and P(2). Each genotype produces a particular proportion of phenotype P(1) (the proportions beimg symbolised by x(1), x(2) and x(3) respectively), and hence proportions 1-x(1), 1-x(2) and 1-x(3) of phenotype P(2) respectively. These values may be represented in tabular form:-

Genotype	Genotype frequency	Proportions of each phenotype from each genotype (i.e. $p(P_A \mid G_B)$	
		P_1	P_2
G_1	f_1	x_1	$(1-x_1)$
G_2	f_2	x_2	$(1-x_2)$
G_3	f_3	x_3	$(1-x_3)$

Let the frequencies of the genotypes be f_1, f_2 and f_3, where f_1, f_2 and f_3 are linked by the Hardy-Weinberg equilibrium. If we assume that G_2 is the heterozygote, then the frequency of one of the alleles, A_1 is clearly:-

$$A_1 = \sqrt{f_1}$$

and hence the frequency of the other allele, A_2, is:

$$A_2 = 1 - \sqrt{f_1}$$

Hence the three genotype frequencies can be represented:-

$$f_1 = A_1^2$$

$$f_2 = 2.A_1.A_2$$

$$f_3 = A_2^2$$

Let L be the incidence of P_1 in the population. Then it is clearly the case that:-

$$L = p(P_1) = \sum_{n=1,3} r_n.f_n \qquad \ldots 1$$

For a particular model, defined by x_1, x_2 and x_3, then since L is known (from the data to be fitted or predicted), and since f_2 and f_3 are expressible in terms of f_1, then f_1 can be determined.

The conditional probabilities $p(G|P)$

In order to calculate the expected offspring from particular parental pairs, it is necessary to know, for an individual, the probability that he is a particular genotype, given that he is a particular phenotype.

In general it may be shown that:-

$$p(G_n|P_m) = \frac{p(G_n).p(P_m|G_n)}{p(P_m)} \qquad \ldots 2$$

where $p(P_m|G_n)$ is the probability of phenotype m given that the genotype is type n, and $p(G_n)$ is equivalent to f_n, the frequency of genotype G_n.

Calculation of family tables, that is $p(P|Q \times R)$

In order to calculate the probability of an individual being a particular phenotype, given the particular phenotypes of his parents, it is necessary to have a function which generates the Mendelian breeding ratios. Let $M(G_a|G_b \times G_c)$ give the probability that for a mating between genotypes G_b and G_c that the progeny will be of genotype G_a. Thus if G_1 and G_3 are the homozygotes, and G_2 the heterozygotes, then from simple Mendelian principles,

$$M(G_2|G_1 \times G_3) = 0.5$$
$$M(G_1|G_2 \times G_3) = 0.25$$
$$M(G_3|G_1 \times G_3) = 0.25$$

Consider two parents of known genotype. In general:-

$$p(P_m|G_a \times G_b) = \sum_{x=1,3} p(P_m|G_x).M(G_x|G_a \times G_b) \qquad \ldots 3$$

But the problem is more typically to calculate the probability of the progeny's phenotype given the parents phenotypes not genotypes. For such a situation one may extend the

above equation 3, so that we may calculate:-

$$p(P_m|P_c \times P_d) = \sum_{y=1,3} \sum_{z=1,3} p(G_y|P_c).p(G_z|P_d).p(P_m|G_y \times G_z) \quad \ldots 4$$

Monozygotic twins

The problem is to calculate $p(P_a \ \& \ P_b)$, that is the proportion of twin-pairs in whom twin 1 is of phenotype a, and twin 2 is of phenotype b. Note that using this notation then to find the proportion of discordant twin-pairs we must remember that:-

$$p(\text{discordant}) = p(P_1 \ \& \ P_2) + p(P_2 \ \& \ P_1) \quad \ldots 5$$

Consider a pair of twins of genotype G_m. Then for these twins:-

$$p(P_a \ \& \ P_b|G_m) = p(P_a|G_m).p(P_b|G_m) \quad \ldots 6$$

(assuming that chance processes occur independently in the two twins).

For the progeny of parents of genotypes G_j and G_k, then:-

$$p(P_a \& P_b|G_j \times G_k) = \sum_{m=1,3} M(G_m|G_j \times G_k).p(P_a|G_m).p(P_b|G_m) \quad \ldots 7$$

Hence for the progeny of parents of known phenotypes:-

$$p(P_a\&P_b \mid P_j x P_k) = \sum_{m=1,3} \sum_{n=1,3} p(P_a\&P_b \mid G_m x G_n).p(G_m \mid P_a).p(G_n \mid P_b) \quad \ldots 8$$

And thus for the total population of MZ twins:-

$$p(P_a\&P_b) = \sum_{j=1,3} \sum_{k=1,3} p(P_a\&P_b \mid P_j x P_k).p(P_j).p(P_k) \quad \ldots 9$$

This equation (9) can however be much simplified. In the total population the genotype frequencies of MZ twins must be the same as in the remaining singleton population. For the calculation of the overall proportions of concordant and discordant pairs irrespective of parental phenotypes, the parental calculations are strictly irrelevant, and:-

$$p(P_a \,\&\, P_b) = \sum_{n=1,3} p(P_a \mid G_n).p(P_b \mid G_n).p(G_n) \quad \ldots 10$$

Dizygotic twins

Using the same notation as for monozygotic twins, but remembering that dizygotic twins do not have the same genotype, but do have the same parents, we may calculate the proportions of concordant and discordant pairs. In making the calculations we must remember that due to the DZ twins having shared parents, $p(G_a \,\&\, G_b)$ is not

the same as $p(G_a).p(G_b)$ (an easy error to make).

Consider parents of genotypes G_m and G_n. Then:-

$$p(P_a\&P_b \mid G_m x G_n) = \sum_{x=1,3} \sum_{y=1,3} m(G_x \mid G_m x G_n).M(G_y \mid G_m x G_n).p(P_a \mid G_x).p(P_b \mid G_y) \quad \ldots 11$$

And thus for parents of known phenotypes:-

$$p(P_a\&P_b \mid P_m x P_n) = \sum_{x=1,3} \sum_{y=1,3} p(P_a\&P_b \mid G_x x G_y).p(G_x \mid P_m).p(G_y \mid p_n) \quad \ldots 12$$

Consequently for the whole population, irrespective of parental phenotype:-

$$p(P_a\&P_b) = \sum_{m=1,3} \sum_{n=1,3} p(P_a\&P_b \mid P_m x P_n).p(P_m).p(P_n) \quad \ldots 13$$

An example

Lest the above equations seem impossibly complex (which they only are as a result of being completely general), a very simple worked example should help to clarify the arguments.

Consider a genetic model in which there are two alleles,

D and C, which produce phenotypes as follows:-

Genotype	Genotype frequency	Phenotypes Left	Right
DD	d^2	0.0	1.0
DC	2dc	0.25	0.75
CC	c^2	0.5	0.5

The above table is thus analogous to that presented earlier in the first part of this appendix.

Let L represent the overall incidence of left-handedness. Then from equation 1:-

$$L = (0).d^2 + (0.25).2dc + (0.5).c^2$$

Since d = 1 - c, then:-

$$L = (0.5).c.(1-c) + (0.5).c^2$$

$$= 0.5 - 0.5c^2 + 0.5c^2 = 0.5c$$

$$\therefore \quad c = 2L$$

The numerical advantage of this particular model is that L is a linear function of c; however for all other models L is a quadratic function of C, which complicates the equations.

We may now re-write the genotype frequencies:-

$$p(CC) = 4L^2$$
$$p(DD) = (1-2L)^2$$
$$p(DC) = 4L(1-2L)$$

From equation 2 we may now calculate the conditional probabilities of a particular genotype given that the person is of a particular phenotype. Thus:-

$$p(DC|L) = \frac{4L(1-2L).(0.25)}{L}$$

$$= 1 - 2L$$

And thus for the rest of the table:-

Genotype	p(Genotype | Left-handed)	p(Genotype | Right-handed)
DD	0	$\frac{(1 - 2L)^2}{(1 - L)}$
DC	$1 - 2L$	$\frac{3L(1 - 2L)}{(1 - L)}$
CC	$2L$	$\frac{2L^2}{(1 - L)}$

In order to calculate the family breeding tables we need to know the Mendelian genetics of the three genotypes; that is, for all combinations of a, b and c, we must know

the value of $p(G_a | G_b \times G_c)$. Simple genetical theory gives us:-

		G(c)		
		DD	DC	CC
G(b)	DD	p(DD)=1.0 p(DC)=0.0 p(CC)=0.0	p(DD)=0.5 p(DC)=0.5 p(CC)=0.0	p(DD)=0.0 p(DC)=1.0 p(CC)=0.0
	DC	p(DD)=0.5 p(DC)=0.5 p(CC)=0.0	p(DD)=0.25 p(DC)=0.5 p(CC)=0.25	p(DD)=0.0 p(DC)=0.5 p(CC)=0.5
	CC	p(DD)=0.0 p(DC)=1.0 p(CC)=0.0	p(DD)=0.0 p(DC)=0.5 p(CC)=0.5	p(DD)=0.0 p(DC)=0.0 p(CC)=1.0

If we wish to calculate $p(L | L \times L)$, then firstly using equation 3:-

$$p(L|DD \times DD)=0.0$$
$$p(L|DD \times DC)=p(L|DC \times DD)=0.125$$
$$p(L|DD \times CC)=p(L|CC \times DD)=0.25$$
$$p(L|DC \times DC)=0.25$$
$$p(L|DC \times CC)=p(L|CC \times DC)=0.375$$
$$p(L|CC \times CC)=0.5$$

These values may then be entered into equation 4, giving:-

$$p(L|L \times L) = \frac{1-2L}{8} + \frac{2L}{4} + \frac{(1-2L)^2}{4} + \frac{4L^2}{2}$$

$$+ 2(1-2L).2L.(0.375)$$

$$= \frac{1+2L}{4} = \frac{1+c}{4}$$

And similarly:-

$$p(L|R \times R) = \frac{3(3-c)}{4(2-c)}$$

$$p(L|R \times L) = \frac{1 + c(2-c)}{4(2-c)}$$

(c is used instead of L as the equations are simpler).

Notice how, despite the complexities of equations 3 and 4, for particular cases there are solutions which are relatively simple. Nevertheless the general equations are rather more complex sinze a). Thev are applicable to any two-allele genetic model, and b), they are particularly suitable for use in a computer, and most persons wishing to carry out such calculations would probably use a computer.

In the particular model being discussed the equati ons for monozygotic twins also reduce to fairly simple results. From equation 10 it can be shown that:-

$$p(L\&L) = c^2.(0.5)^2 + 2dc.(0.25)^2 + d^2.(0.0)^2$$

$$= \frac{c^2}{2} + \frac{2dc}{16}$$

$$= \frac{c^2}{2} + \frac{dc}{8}$$

Similarly, it can be shown that:-

$$p(R\&R) = d^2 = \frac{9dc}{8} + \frac{c^2}{2}$$

$$p(R\&L \text{ or } L\&R) = \frac{c^2}{2} + \frac{3dc}{4}$$

If the reader has progressed thus far in replicating the above equations then he will surely understand the (relatively simple) principles involved, and thus there will be no need to produce an exact solution for the numerically more complex case of the dizygotic twins.

Corrections for actual incidence of left-handedness not equalling true incidence

The measured incidence of left-handedness in most of the studies being used as a data-base is different, both within studies between parents and children, and also between studies within a particular generation. These differences might possibly represent real differences in allele frequency, and that would be the classic genetic approach to such discrepancies (and indeed is the approach which I have used elsewhere in fitting the hand-clasping data and arm-folding data, where there is good reason to believe that response biasses and criterion shifts are of little significance). However, in the case of handedness there is reason to be doubtful and I will assume that the true incidence of left-handedness is in fact constant, and that differences in apparent or manifest incidence are due instead to alterations in the criterion of left-handedness, or to differences in response rates of right and left-handers to questionnaires, etc. Annett (1978,1979) has shown how by varying the criterion of left-handedness widely differing incidences of 'left-handedness' can be obtained.

I would of course dispute that many of these scales are truly measuring left-handedness, and would argue that the criterion put forward elsewhere, of writing hand alone, is probably the best criterion. Nevertheless there are still such shifts in other data and instead of simply discarding unacceptable data (the approach of Levy and Nagylaki, 1972), I will instead attempt to correct for these biasses.

The main types of error, which I will call criterion shifting and response bias, do not, regrettably, have identical corrections. And for criterion shifting it is not strictly possible, on logical and arithmetic grounds, to say that there is even a single correction.

Despite all such problems I will nevertheless attempt to fit the data bearing in mind that some small discrepancies may still be present and be essentially irremovable.

A further complication to be borne in mind is that the corrections need not be the same type, nor in the same direction, nor of the same magnitude, in parents and children.

Notation

Let the true handedness, H, be notated as H_t and the manifest handedness as H_m, where H can be either R or L

specifically, or 'H', meaning either phenotype.

Corrections for simple criterion shift when $p(L_m) < p(L_t)$

This is very simple. For any individual who is truly left-handed there is a finite probability, q, that he will manifest as a right-hander, hence:-

$$p(L_m) = q.p(L_t) \qquad \text{where } q = \frac{p(L_m)}{p(L_t)} \qquad \ldots 14$$

More importantly, since the correction is indepeddent of propositus genotype, or of parental phenotype or genotype, then for any given population subset:-

$$p(L_m \mid \text{subset}) = q.p(L_t \mid \text{subset})$$

and particularly:-

$$p(L_m \mid H_a x H_b) = q.p(L_t \mid H_a x H_b)$$ where H_a and H_b are both true handedness ... 15

For monozygotic twins a similar correction may be made:-

$$p(L_m \,\&\, L_m) = q^2.p(L_t \,\&\, L_t)$$

$$p(R_m \,\&\, R_m) = (1-q)^2.p(L_t \,\&\, L_t) + 2q.(1-q).p(L_t \,\&\, L_t) + p(R_t \,\&\, R_t)$$

$$p(R_m \,\&\, L_m) = 1. - p(L_m \,\&\, L_m) - p(R_m \,\&\, R_m)$$

Corrections for criterion shifting when $p(L(m)) > p(L(t))$

This is basically similar to the previous case, although it is not immediately obvious that it is valid to use the same equation with $q > 1.0$. The situation is that there is now a finite probability, r, that a true right-hander will manifest as a left-hander, all true left-handers being presumed to manifest as left-handers. Hence:-

$$p(R_m) = r.p(R_t) \quad \text{where} \quad r = \frac{p(R_m)}{p(R_t)} \qquad \ldots 16$$

Using the same argument as before:-

$$p(R_m \mid H_a \times H_b) = r.p(R_t \mid H_a \times H_b)$$

And thus:-

$$p(L_m \mid H_a \times H_b) = 1 - r.(1 - p(L_m \mid H_a \times H_b)) \qquad \ldots$$

If equation 17 is identical to equation 15 (i.e. if it is valid to use $q > 1$ in equation 15), then we would expect that:-

$$p(L_m \mid H_A \times H_B) = 1 - r(1 - p(L_t \mid H_A \times H_B)) = q.p(L_t \mid H_A \times$$

..

Expanding the second part of equation 18, and substituting $T = p(L(t)\,|\,H(A)xH(B))$ and $M=p(L(m)\,|\,H(A)xH(B))$, then:-

$$1 - r(1-T) = q.T \qquad \ldots 18a$$

From equation 14 we know that $M = qT$, and from equation 16 that $r=p(R(m))/p(R(t))$, and these may be substituted into equation 18a, to produce:-

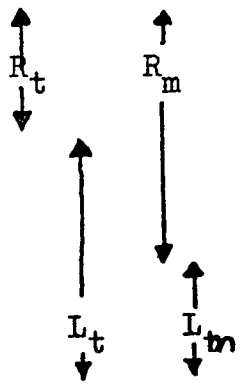
$$1 - \frac{(1-qT)}{(1-T)}.(1-T) = q.T$$

which is an identity. Hence equation 14 is valid both for $q < 1$ and $q > 1$.

Corrections for differences in parental left-handedness incidence

Thus far, corrections have only been made for $p(L_m)$ not being equal to $p(L_t)$ in the progeny. Parents however may also have incidences of left-handedness which are different to those of the true incidence, and corrections must also be made for this as well. The corrections are best seen by setting out a 3 x 3 matrix.

Consider firstly the case in which $p(L_{m-par}) > p(L_t)$:-



	R_t & R_m	L_t & R_m	L_t & L_m	Frequency
R_t & R_m	R_t x R_t	R_t x L_t	R_t x L_t	$p(R_t)$
L_t & R_m	R_t x L_t	L_t x L_t	L_t x L_t	$(1-s).p(L_t$
L_t & L_m	R_t x L_t	L_t x L_t	L_t x L_t	$s.p(L_t)$

From this diagram, in which true left-handers are divided into two types, manifest left-handers (L_t & L_m), and manifest right handers (L_t & R_m), it is simple to write down correction equations: Let $s=p(L_m)/p(L_t)$. Then:-

$$p(L_t|R_m x R_m)=\left[p(R_t)^2.p(L_t|R_t x R_t)+2.p(R_t)(1-s).p(L_t).p(L_t|R_t x L_t)\right.$$

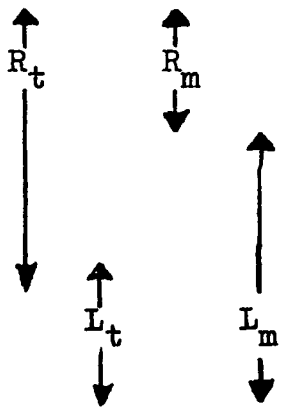
$$\left.+(1-s)^2.p(L_t)^2.p(L_t|L_t x L_t)\right]/(1-s.p(L_t)^2) \qquad \ldots 19$$

$$p(L_t|R_m x L_m)=\frac{\left[p(R_t).s.p(L_t).p(L_t|R_t x L_t)+s.p(L_t)^2.(1-s).p(L_t|L_T x L_t)\right]}{(1-s.p(L_t)).s.p(L_t)} \qquad \ldots 20$$

$$p(L_t|L_m \text{ x } L_m) = p(L_t|L_t \text{ x } L_t) \qquad \ldots 21$$

Alternatively consider the case in which $p(L_{m-par}) > p(L_t)$ It is now assumed that this is entirely due to true right-

handers manifesting as left-handers. Let $u = p(R_m)/p(R_t)$. Constructing a similar table to the previous one, thus:-



	R_t & R_m	R_t & L_m	L_t & L_m	Frequenc
R_t & R_m	$R_t \times R_t$	$R_t \times R_t$	$R_t \times R_t$	$u.p(R_t)$
R_t & L_m	$R_t \times R_t$	$R_t \times R_t$	$R_t \times L_t$	$(1-u).p(R$
L_t & L_m	$R_t \times L_t$	$R_t \times L_t$	$L_t \times L_t$	$p(L_t)$

And once more reading off directly from the table, we may see that:-

$$p(L_t \mid R_m \times R_m) = p(L_t \mid R_t \times R_t) \qquad \ldots 22$$

$$p(L_t \mid R_m \times L_m) = p(L_t \mid R_t \times L_t) + \frac{(1-u).p(R_t).p(L_t \mid R_t \times R_t)}{p(L_t)} \qquad \ldots 23$$

$$p(L_t \mid L_m \times L_m) = \frac{((1-u).p(R_t).p(L_t \mid R_t \times R_t) + 2.p(R_t).(1-u).p(L_t).p(L_t \mid R_t \times L_t) + p(L_t).p(L_t \mid L_t \times L_t)}{(1 - u.p(R_t))} \qquad \ldots 24$$

Scrutiny of equations 22 to 24 will reveal, unlike the case of the progeny, described earlier, that the correction for $p(L_m)/p(L_t)$ being greater than 1 cannot be the same as that when the value is less than 1. Consider equations 19 and 22. Equation 19 is a function of s; equation 22 is independent of s. But if in equation 19, s were greater than 1, $p(L_t \mid R(m) \times R(m))$ must still be a function of s. Hence equations 19 and 22 cannot be alternative views of the same equations, and hence two separate sets of corrections must therefore be used for the situations in which $s > 1$ and $s < 1$.

Of course if the exact proportions were known for the two processes represented by the values s and u, then an exact correction could be made for the occurrence of both processes. But in general such information will not be available.

Since both parents and children will probably have $p(L_m)$ differrnt from $p(L_t)$, the procedure used in the calculations was firstly to correct for the parents, using equations 19 to 24 and then to correct for the children (using equation 15).

Corrections for response bias amongst propositus

Consider a population of right and left-handed propositi. Left-handers do not respond as often as right-

handers, only a proportion, k, of the true left-handers responding, whilst all of the right-handers respond. (The argument is the same if only x of the right-handers respond, and only kx of the left-handers respond; the corrections are needed whenever k is not equal to 1).

We may represent the situation thus:-

	L_t		R_t
	non-responders	responders	responders
prop'n	$(1-k).p(L_t)$	$k.p(L_t)$	$p(R_t)$

The ratio of $p(L_m)$ to $p(L_t)$ may be represented by j, where:- $j = p(L_m)/P(L_t)$. It may readily be shown that:-

$$j = \frac{k}{k.p(L_t) + p(R_t)} \qquad \ldots 25$$

Consider progeny of a particular parental phenotype, H x I. Then:-

$$p(L_m|H \times I) = \frac{k.p(L_t|H \times I)}{k.p(L_t|H \times I) + p(R_t|H \times I)} \qquad \ldots 26$$

It is tempting to hope that this equation, 26, might be identical to equation 15, so that expressing equation 26 in terms of j would result in an equation of the form:-

$$p(L_m \mid H \times I) = z.p(L_t \mid H \times I) \qquad \ldots 27$$

Consideration however shows that this cannot be so. Let there exist an equation of the following form for R x R matings (derived fromequation 27).

$$p(L_m \mid R \times R) = z.p(L_t \mid R \times R)$$

But also, from equation 26:-

$$p(L_m \mid R \times R) = \frac{k.p(L_t \mid R \times R)}{k.p(L_t \mid R \times R) + p(R_t \mid R \times R)}$$

And hence:-

$$z.p(L_t \mid R \times R) = \frac{k.p(L_t \mid R \times R)}{k.p(L_t \mid R \times R) + p(R_t \mid R \times R)}$$

$$z = \frac{k}{k.p(L_t \mid R \times R) + p(R_t \mid R \times R)}$$

Thus z is a function of $p(L_t \mid RxR)$. If therefore z were valid for finding $p(L_m \mid RxL)$ and $p(L_m \mid LxL)$, these would also involve functions of $p(L_t \mid RxR)$; but this clearly contradicts the form of equation 27, and hence we may presume that no such equation can possibly exist.

Hence we may infer that corrections for criterion shift and corrections for response bias are <u>not</u> the same. How

different they are in practice is a question best examined by actual examples.

Consider a population in which $p(L_t) = 0.10$, and $p(L_m)$, due to a response bias, is 0.08. Then $j = 0.8$, and thus $k = 0.7826$. Let $p(L_t \mid R \times R)$ be 0.08. Then using the correction as in equation 26, $p(L_m \mid R \times R)$, = 0.0637, whereas using a correction as in equation 15, $p(L_m \mid R \times R) = 0.0640$.

Similarly for a value of $p(L_t \mid L \times L)$ of 0.35, the respective values of $p(L_m \mid L \times L)$ are 0.2964 and 0.2800.

Thus in general the predictions only really differ when $p(L_T \mid H \times I)$ is quite a lot greater than $p(L_t)$, but this only occurs, of course, for L x L matings, which are themselves relatively rare. The implication is that for most purposes the correction of equation 15 will be adequate.

As with the discussion earlier for a criterion shift, so it is not immediately clear that equation 26 is valid both for $p(L_m) > p(L_t)$, and for $p(L_m) < p(L_t)$. We may represent the situation in which there is a relative proportion of right-handers who do not respond, as

Proportion	L_t	R_t	
	responders $p(L_t)$	responders $f.p(R_t)$	non-responders $(1-f).p(R_t)$

We may then find:-

$$e = \frac{p(L_m)}{p(L_t)} = \frac{1}{p(L_t) + f.p(R_t)} \qquad \ldots 28$$

and hence:-

$$p(L_m \mid H \times I) = \frac{p(L_t \mid H \times I)}{p(L_t \mid H \times I) + f.p(R_t \mid H \times I)} \qquad \ldots 29$$

We may thus combine equations 26 and 29, since both equal $p(L_m \mid H \times I)$.

$$\therefore \frac{p(L_t \mid H \times I}{p(L_t \mid H \times I) + f.p(P_t \mid H \times I)} = \frac{k.p(L_t \mid H \times I)}{k.p(L_t \mid H \times I) + p(R_t \mid H \times I)}$$

$\ldots 30$

Inserting values for f and k from equations 25 and 28 respectively, it may be shown that the equation eventually reduces to the form, j = e. Hence equation 26 is valid whether $p(L_m)$ is greater than or less than $p(L_t)$.

To show the magnitude of such corrections, consider the situation in which $p(L_t) = 0.10$, and $p(L_m) = 0.20$. Then $j = 2.0$ and thus $k = 2.250$. If $p(L_t \mid R \times R) = 0.08$, then $p(L_m \mid R \times R) = 0.1636$ by the response bias method, or

0.1800 by the criterion shift method. Onee again the differences are relatively small, and I would like to propose that they can probably be ignored.

Corrections for response bias amongst parents

These are not strictly relevant since in most studies, a) the propositi respond, not the parents, b) it is unlikely that students with left-handed parents show a different response rate to those without, and c) the parental incidence of sinistrality in most studies is fairly low, and suggests that criterion shifts are probably of greater import.

In general the effects of differing parental incidences (of whatever sort) are relatively small in comparison with the effects due to propositus biasses, and thus differences in mode of parental correction are unlikely to reduce large effects. They will not be considered in further detail here,

APPENDIX A7:3: ASSORTATIVE MATING FOR HANDEDNESS

Assortative mating is the situation in which like preferentially mates with like (positive assortative mating), or like preferentially mates with non-like (negative assortative mating). Chance expectations for non-assortative mating may be obtained from population phenotype frequencies and from the binomial or multinomial distribution. If assortative mating is present then account must be taken of that fact in the calculation of expected frequences in progeny, etc. (see Cavalli-Sforza and Bodmer, 1971, p58, pp537-550 for a review).

Table 7.76 shows the proportions of R-R, R-L and L-L matings in various studies from the literature. These data sets are shown graphically in Figure 7.14. Table 7.7 also shows the Chi-squared value for the goodness of fit of a binomial distribution (note that in some of these cases the expected values are less than one, and thus care should be taken in interpreting these values). Of the thirteen data sets, six shows less R-L pairings than would be expected, and seven show more than would be expected. Four of the sets showing positive assortative mating are significantly different from chance expectations with $p < 0.05$, whilst only one of the sets showing negative assortative matings is significant at the 0.04 level. Of the significant cases of positive assortative mating, one is the Hicks and Kinsbourne (1976) study, which, as will be shown

in Chapter 10, shows several strange features, and should perhaps not be treated too seriously. Of the remaining studies, there seems little doubt that overall the data is heterogeneous, differing from a binomial distribution; but the fact that these differences are not in a consistent direction suggests that some factors other than assortative mating may be the cause. A response bias may easily produce a surplus of 'unusual' or 'interesting' families, such as those with two left-handed parents.

In summary, there is a significant heterogeneity amongst the parental mating pairs but this difference from predicted proportions is relatively small, and may well not be the result of true assortative mating. For the purposes of model fitting, it may safely be ignored until it is demonstrated more convincingly.

Table 7.1

Shows the data from fourteen studies of the incidence of left-handedness in families of different parental types. Column 1 gives the name of the study; columns 2 and 3 indicate the overall incidence of left-handedness in the propositi and in the parents; columns 4 and 5 and 6 show the proportion of left-handers, and the actual numbers of right and left-handers in the progeny of R x R matings, the top figure indicating the actual values, and the figures in brakkets indicating the predictions of the model, the first figure in the brakkets being for a model in which $p(L_t) = 0.08$ and $p(L|DC) = 0.125$, and the second figure being for a model in which $p(L_t) = 0.095$, and $p(L|DC) = 0.25$; column 7 gives the value of the Chi-squared goodness of fit statistic for the two models, for just the R x R data; columns 8 - 11 give similar information for R x L matings, and columns 12 - 15 for L x L matings; the final column gives the total Chi-squared values for the goodness of fit.

RxR

Study	p(L) propositi	p(L) parents	p(L)	n(R)	n(L)	Chi^2
ICM-2 grandparents	3.22	3.31	2.15 (2.98,2.99)	455 (451.1,451.1)	10 (13.9,13.9)	(1.118
Chamberlain (1928)	4.77	3.56	4.26 (4.39,4.40)	6917 (6907.5,6907.0)	308 (317.5,318.0)	(0.298
ICM-1 parents	6.66	6.10	2.91 (5.74,5.76)	167 (162.1,162.1)	5 (9.9,9.9)	(2.548
Mascie-Taylor (1977)	8.30	9.30	6.82 (6.49,6.81)	232 (232.9,232.0)	17 (16.1,17.0)	(0.048
Annett (1978) OU	8.50	5.47	7.27 (7.45,7.48)	1656 (1652.9,1652.4)	130 (133.1,133.6)	(0.077
ICM-2 parents	8.53	4.55	7.68 (7.66,7.68)	1924 (1924.3,1923.9)	160 (159.7,160.1)	(0.000
Rife (1940)	8.76	5.24	7.57 (7.73,7.75)	1842 (1839.0,1838.5)	151 (154.0,154.5)	(0.064
Ferronato (1974)	9.75	9.86	6.66 (7.57,8.00)	154 (152.5,151.8)	11 (12.5,13.2)	(0.192
Annett (1972)	10.63	4.40	9.73 (9.67,9.69)	6206 (6209.9,6208.6)	669 (665.1,666.4)	(0.025
Chaurasia & Goswami	14.07	10.40	11.96 (10.92,11.55)	1060 (1072.5,1064.9)	144 (131.5,139.1)	(1.33
ICM-2 propositi	14.39	9.82	11.35 (11.17,11.81)	796 (797.9,791.9)	102 (110.3,106.1)	(0.03
Hubbard (1971)	14.58	6.30	13.94 (12.49,12.55)	722 (734.2,733.7)	117 (104.8,105.3)	(1.62
Ramaley (1913)	15.56	8.03	12.03 (12.66,12.77)	841 (834.9,833.9)	115 (121.1,122.1)	(0.
ICM-1 propositi	15.69	9.66	13.51 (12.18,12.88)	755 (766.7,760.6)	118 (106.3,112.4)	(1.
Combined LxL data I	8.73	6.36				
Combined LxL data II	14.84	8.84				

)	Chi^2	RxL p(L)	RxL n(R)	LxL n(L)	LxL Chi^2	LxL p(L)	LxL n(R)	LxL n(L)	LxL Chi^2
		18.75	26	6					
3.9,13.9)	(1.118,1.128)	(6.53,6.44)	(29.9,29.9)	(2.1,2,1)	(7.819,8.050)	(10.08,12.05)	0	0	
3		11.42	411	53		28.0	18	7	
17.5,318.0)	(0.298,0.330	(9.67,9.52)	(419.1,419.8)	(44.9,44.2)	(1.639,1.956)	(14.94,17.85)	(21.3,20.5)	(3.7,4.5)	(3.357,1.755)
		25.0	15	5			0	3	
.9,9.9)	(2.548,2.583)	(13.30,12.97)	(18.3,17.4)	(2.7,2.6)	(2.376,2.562)	(20.86,24.93)			
		14.58	41	7			3	1	
6.1,17.0)	(0.048,0.000)	(16.24,16.97)	(40.2,39.9)	(7.8,8.1)	(0.097,0.194)	(25.99.26.93)			
0		19.04	170	40			4	0	
33.1,133.6)	(0.077,0.102)	(17.03,16.66)	(174.2,175.0)	(35.8,35.0)	(0.602,0.863)	(26.62,31.81)			
0		18.23	148	33			7	1	
59.7,160.1)	(0.000,0.001)	(17.19,16.86)	(149.9,150.5)	(31.1,30.5)	(0.139,0.241)	(26.71,31.92)			
1		19.54	140	34			5	6	
54.0,154.5)	(0.064,0.086)	(17.58,17.21)	(143.4,144.1)	(30.6,29.9)	(0.461,0.665)	(27.43,32.79)			
		22.50	31	9			0	0	
2.5,13.2)	(0.192,0.400)	(19.34,20.50)	(32.3,31.8)	(7.7,8.2)	(0.255,0.098)	(29.68,29.99)			
)		20.97	471	125			5	1	
5.1,666.4)	(0.025,0.011)	(21.48,21.11)	(468.0,470.2)	(128.0,125.8)	(0.091,0.007)	(33.29,39.78)			
		27.38	122	46			3	4	
1.5,139.1)	(1.334,0.199)	(28.53,30.35)	(120.1,117.0)	(47.9,51.0)	(0.108,0.701)	(41.19,41.32)			
		25.75	173	60			6	2	
.3,106.1)	(0.032,0.177)	(28.50,30.19)	(166.6,162.7)	(66.4,70.3)	(0.864,2.181)	(43.94,44.43)			
		19.01	90	23			0	0	
.8,105.3)	(1.626,1.494)	(29.07,28.34)	(85.8,86.7)	(35.2,34.3)	(5.945,5.193)	(45.66,54.57)			
5		32.33	113	54			1	7	
21.1,122.1)	(0.347,0.474)	(30.70,,29.79)	(115.7,117.3)	(51.3,49.7)	(0.211,0.519)	(48.73,58.00)			
8		25.65	142	49					
06.3,112.4)	(1.460,0.316)	(30.86,32.65)	(132.1,128.6)	(58.9,62.4)	(2.427,4.256)	(48.52,			
						33.3			
						(27.34,			
						43.4			
						(46.50			

RxL

	Chi^2	p(L)	n(R)	n(L)	Chi^2	p(I
,13.9)	(1.118,1.128)	18.75 (6.53,6.44)	26 (29.9,29.9)	6 (2.1,2.1)	(7.819,8.050)	(1(
5,318.0)	(0.298,0.330	11.42 (9.67,9.52)	411 (419.1,419.8)	53 (44.9,44.2)	(1.639,1.956)	28 (1·
9.9)	(2.548,2.583)	25.0 (13.30,12.97)	15 (18.3,17.4)	5 (2.7,2.6)	(2.376,2.562)	(2
,17.0)	(0.048,0.000)	14.58 (16.24,16.97)	41 (40.2,39.9)	7 (7.8,8.1)	(0.097,0.194)	(2
,133.6)	(0.077,0.102)	19.04 (17.03,16.66)	170 (174.2,175.0)	40 (35.8,35.0)	(0.602,0.863)	(
,160.1)	(0.000,0.001)	18.23 (17.19,16.86)	148 (149.9,150.5)	33 (31.1,30.5)	(0.139,0.241)	
,154.5)	(0.064,0.086)	19.54 (17.58,17.21)	140 (143.4,144.1)	34 (30.6,29.9)	(0.461,0.665)	
13.2)	(0.192,0.400)	22.50 (19.34,20.50)	31 (32.3,31.8)	9 (7.7,8.2)	(0.255,0.098)	
,666.4)	(0.025,0.011)	20.97 (21.48,21.11)	471 (468.0,470.2)	125 (128.0,125.8)	(0.091,0.007)	
,139.1)	(1.334,0.199)	27.38 (28.53,30.35)	122 (120.1,117.0)	46 (47.9,51.0)	(0.108,0.701)	
3,106.1)	(0.032,0.177)	25.75 (28.50,30.19)	173 (166.6,162.7)	60 (66.4,70.3)	(0.864,2.181)	
8,105.3)	(1.626,1.494)	19.01 (29.07,28.34)	90 (85.8,86.7)	23 (35.2,34.3)	(5.945,5.193)	
1.1,122.1)	(0.347,0.474)	32.33 (30.70,,29.79)	113 (115.7,117.3)	54 (51.3,49.7)	(0.211,0.519)	
6.3,112.4)	(1.460,0.316)	25.65 (30.86,32.65)	142 (132.1,128.6)	49 (58.9,62.4)	(2.427,4.256)	

		LxL		
Chi^2	p(L)	n(R)	n(L)	Chi^2
(7.819,8.050)	(10.08,12.05)	0	0	
(1.639,1.956)	28.0 (14.94,17.85)	18 (21.3,20.5)	7 (3.7,4.5)	(3.357,1.755)
(2.376,2.562)	(20.86,24.93)	0	3	
:0.097,0.194)	(25.99.26.93)	3	1	
0.602,0.863)	(26.62,31.81)	4	0	
0.139,0.241)	(26.71,31.92)	7	1	
0.461,0.665)	(27.43,32.79)	5	6	
0.255,0.098)	(29.68,29.99)	0	0	
0.091,0.007)	(33.29,39.78)	5	1	
0.108,0.701)	(41.19,41.32)	3	4	
0.864,2.181)	(43.94,44.43)	6	2	
5.945,5.193)	(45.66,54.57)	0	0	
(0.211,0.519)	(48.73,58.00)	1	7	
(2.427,4.256)	(48.52,49.19)	0	0	
	33.3 (27.34,32.67)	24 (26.2,24.2)	12 (9.8,11.8)	(0.651,0.007)
	43.4 (46.50,50.50)	10 (12.3,11.4)	13 (10.7,11.6)	(0.928,0.334)

n data, the observed and expected numbers of each type (
cted values (E) are for two different models, 'a' in which p(L)=0.095 and p(L DC)=0.25,
DC)=0.125.

		Monozygotic twins			
y	p(L)	N(R-R) E(a,b)	N(R-L) E(a,b)	n(L-L) E(a,b)	Chi2 (a,b)
ens (1924)	16.21	26 (26.5,26.4)	10 (8.8, 9.0)	1 (1.5,1.4)	0.045,0.027
z (1924)	25.00	10 (10.3,10.3)	7 (6.2,6.3)	1 (1.3,1.3)	0.029,0.030
erbach (1925)	5.33	67 (67.6,67.7)	8 (6.6,6.5)	0 (0.6,0.7)	0.067,0.083
berg (1926)	14.49	53 (51.6,51.3)	12 (14.7,15.2)	4 (2.6,2.3)	1.250,1.815
chuer (1927)	20.28	156 (158.6,157.9)	77 (71.6,73.1)	11 (13.6,12.9)	0.973,0.517
an (1928)	31.00	25 (24.3,24.2)	19 (20.2,20.5)	6 (5.3,5.2)	0.171,0.240
ch (1930)	20.93	25 (27.5,27.4)	18 (12.9,13.2)	0 (2.5,2.4)	4.696,4.313
on & Jones (1932)	10.71	56 (57.1,56.8)	13 (10.8,11.3)	1 (2.1,1.8)	1.070,0.066
ks (1933)	9.52	35 (35.2,35.0)	6 (5.6,5.9)	1 (1.2,1.0)	0.006,0.000
an, Freeman and inger (1937)	19.00	34 (33.5,33.4)	13 (13.8,14.2)	3 (2.6,2.4)	0.127,0.246
erwek (1938)	18.85	80 (82.2,81.8)	38 (33.6,34.3)	4 (6.2,5.8)	1.443,1.010
(1940)	11.88	176 (177.2,176.4)	41 (38.6,40.3)	6 (7.2,6.4)	0.366,0.037
ss (1946)	18.44	72 (70.1,69.8)	24 (27.8,28.4)	7 (5.1,4.8)	1.258,1.789
e (1950)	12.82	261 (266.7,265.5)	76 (64.5,66.9)	6 (11.8,10.5)	5.013,3.227
haume (1957)	24.24	19 (19.4,19.3)	12 (11.2,11.4)	2 (2.4,2.3)	0.122,0.071
zo (1960)	13.32	199 (199.2,198.2)	51 (50.7,52.6)	9 (9.2,8.2)	0.005,0.121
ter-Saltzmann et al 76)	17.11	132 (131.5,130.8)	46 (47.0,48.3)	9 (8.5,7.9)	0.054,0.276
hlin & Nichols (1976)	14.10	380 (338.1,386.3)	123 (106.7,110.4)	11 (19.2,17.3)	6.107,3.83

rs of each type of twin-pair (R-R, R-L and L-L). The
nd p(L DC)=0.25, and 'b' in which p(L)=0.08, and

		Dizygotic twins			
Chi2 (a,b)	p(L)	N(R-R) E(a,b)	N(R-L) E(a,b)	N(L-L) E(a,b)	Chi2 (a,b)
0.045,0.027	27.41	16 (16.5,16.4)	13 (11.9,12.0)	2 (2.5,2.4)	0 0.216,0.177
0.029,0.030	-	-	-		
0.067,0.083	12.69	96 (97.1,96.8)	28 (25.6,26.2)	2 (3.1,2.8)	0.648,0.382
1.250,1.815	7.03	111 (111.3,111.3)	16 (15.4,15.3)	1 (1.3,1.3)	0.006,0.008
0.973,0.517	14.04	136 (133.1,132.6)	34 (39.9,40.7)	8 (5.1,4.6)	2.649,3.600
0.171,0.240	17.00	35 (34.8,34.7)	13 (13.3,15.2)	2 (1.8,1.7)	0.002,0.006
4.696,4.313	6.03	51 (51.4,51.5)	7 (6.1,6.1)	0 (0.4,0.5)	0.032,0.035
1.070,0.066	11.38	97 (97.7,97.4)	24 (22.5,23.1)	2 (2.7m2.4)	0.293,0.110
0.006,0.000	10.63	76 (75.9,75.7)	12 (16.2,16.6)	2 (1.9,1.7)	0.000,0.005
0.127,0.246	11.00	39 (40.1,39.9)	11 (8.8,9.1)	0 (1.1,0.9)	0.143,0.119
1.443,1.010	17.14	23 (24.3,24.2)	12 (9.4,9.5)	0 (1.3,1.2)	0.231,0.205
0.366,0.037	15.41	104 (105.7,105.4)	39 (35.6,36.3)	3 (4.7,4.4)	0.961,0.656
1.258,1.789	16.27	60 (60.9,60.8)	24 (22.0,22.4)	2 (3.0,2.8)	0.519,0.354
.5) 5.013,3.227	11.61	164 (166.7,166.3)	45 (39.4,40.5)	2 (4.8,4.3)	2.448,1.751
) 0.122,0.071	19.69	21 (21.5,21.5)	11 (9.9,10.0)	1 (1.6,1.5)	0.037,0.028
) 0.005,0.121	10.89	264 (269.1,268.3)	69 (58.8,60.4)	2 (7.1,6. 3)	5.530,4.198
) 0.054,0.276	19.31	115 (115.9,115.6)	54 (52.2,52.8)	7 (7.9,7.6)	0.176,0.068
'.3) 6.107,3.830	11.11	261 (266.2,265.4)	70 (59.6,61.2)	2 (7.2,6.4)	5.673,4.348

Table 7.3

This shows a simple summary of the critical features of the main genetic models which have been proposed, including the present one.

Study	Phenotypes				
	Right			Left	
Ramaley (1913)	RR	RL		LL	
Trankell (1955)	RR	RL	(1-x) LL	x LL	
Rife (1950)		RR	(1-x) L	xRL	LL
			'Mixed'		
Annett (1964)		RR	RL	LL	
Levy & Nagylaki (1972)	CC:LL	CC:Ll	CC:ll	Cc:ll	
	Cc:LL	Cc:Ll	cc:LL	cc:ll	
	cc:ll				
	(L,l = Left/right language dominance)				
	(C,c = Contra/ipsi-lateral hand control)				
Annett (1972)	RS+	(RS-)	RS-	(RS+)	
McManus	DD	DC	DC	CC	

Table 7.4

Proportion of individuals of each genotype, by handedness and parental handedness, for a p(L-true) of 9.5%, and additive inheritance.

Parental type	p(DD)	p(DC)	p(CC)
		Handedness not known	
R x R	.72677923	.25146843	.02175223
R x L	.34526797	.56697715	.08775397
L x L	.16402560	.48195500	.35402500
NK	.65610000	.30780000	.03610000
		Right-handers	
R x R	.78464120	.20361667	.01174201
R x L	.42396487	.52215615	.05387786
L x L	.23348750	.51453737	.25197509
NK	.72497200	.25508300	.01994500
		Left-handers	
R x R	0.0	.8525137O	.14748630
R x L	0.0	.76362093	.23637900
L x L	0.0	.40500000	.59500000
NK	0.0	.81000000	.19000000

Table 7.5

Shows, the predicted proportions of the various types of twin pair, for monozygotic twins, by parental handedness.

Pair type / parental type	R - R	R - L	L - L
R x R	87.37	10.52	2.11
R x L	68.61	25.65	5.74
L x L	52.37	35.77	11.86
NK	83.82	13.34	2.82

Table 7.6

Shows the expected genotype probabilities for an individual from a monozygotic twin pair, according to the ty of the twin pair, and the parental handedness type.

Genotype	DD	DC	CC
		R-R pairs	
Pate-ntal type			
R x R	.8317	.1618	.0062
R x L	.5032	.4648	.0319
L x L	.3131	.5174	.1690
N^K	.7826	.2064	.0107
		R-L pairs	
R x R	0.0	.8966	.1034
R x L	0.0	.8289	.1711
L x L	0.0	.5051	.4948
NK	0.0	.8647	.1352
		L-L pairs	
R x R	0.0	.7429	.2570
R x L	0.0	.6176	.3823
L x L	0.0	.2539	.7460
NK	0.0	.6806	.3194

Table 7.7

Shows the observed values of the numbers of R-R, R-L and L-L matings in the parents of various study populations. The table also shows the total number of parental pairs (n), the overall parental incidence of left-handedness (p(L)), and the Chj-squared value for the goodness of fit of a binomial distribution.

Study	R-R	R-L	L-L	n	p(L)	Chi2
II: grandparents	465	32	0	497	3.21%	0.55
Chamberlain (1928)	2031	137	9	2177	3.55%	15.18
Annett (1973)	1978	171	2	2151	4.06%	0.74
II: parents	766	67	4	837	4.48%	3.50
Rife (1940)	620	62	5	687	5.24%	5.76
I: parents	172	20	3	195	6.66%	6.03
Mascie-Taylor (1978)	163	29	1	193	8.03%	0.07
Ramaley (1915)	258	45	2	305	8.03%	0.01
Hicks & Kinsbourne (1976) - biological parents	923	150	28	1101	9.35%	42.58
I: propositi	337	81	0	418	9.68%	4.81
II: propositi	351	79	3	433	9.81%	0.40
Ferronato et al (1974)	61	15	0	76	9.86%	0.91
Hicks & Kinsbourne (1976) - step-parents	54	39	15	108	31.94%	3.10

Figure 7.1 Shows the family data of Table 1 plotted, separately for the progeny of R x R, R x L and L x L matings, as a function of the overall incidence of left-handedness in the particular study. Data points are plotted plus or minus one standard error. R x R progeny are plotted as small filled circles, R x L progeny as open circles, and L x L progeny as filled squares. In view of the small numbers of L x L matings, several groups of studies have been combined, as indicated by the two large inclusion brackets. The abscissa represents the population incidence of left-handedness, and the ordinate represents the percentage of left-handedness in the particular progeny type being shown.

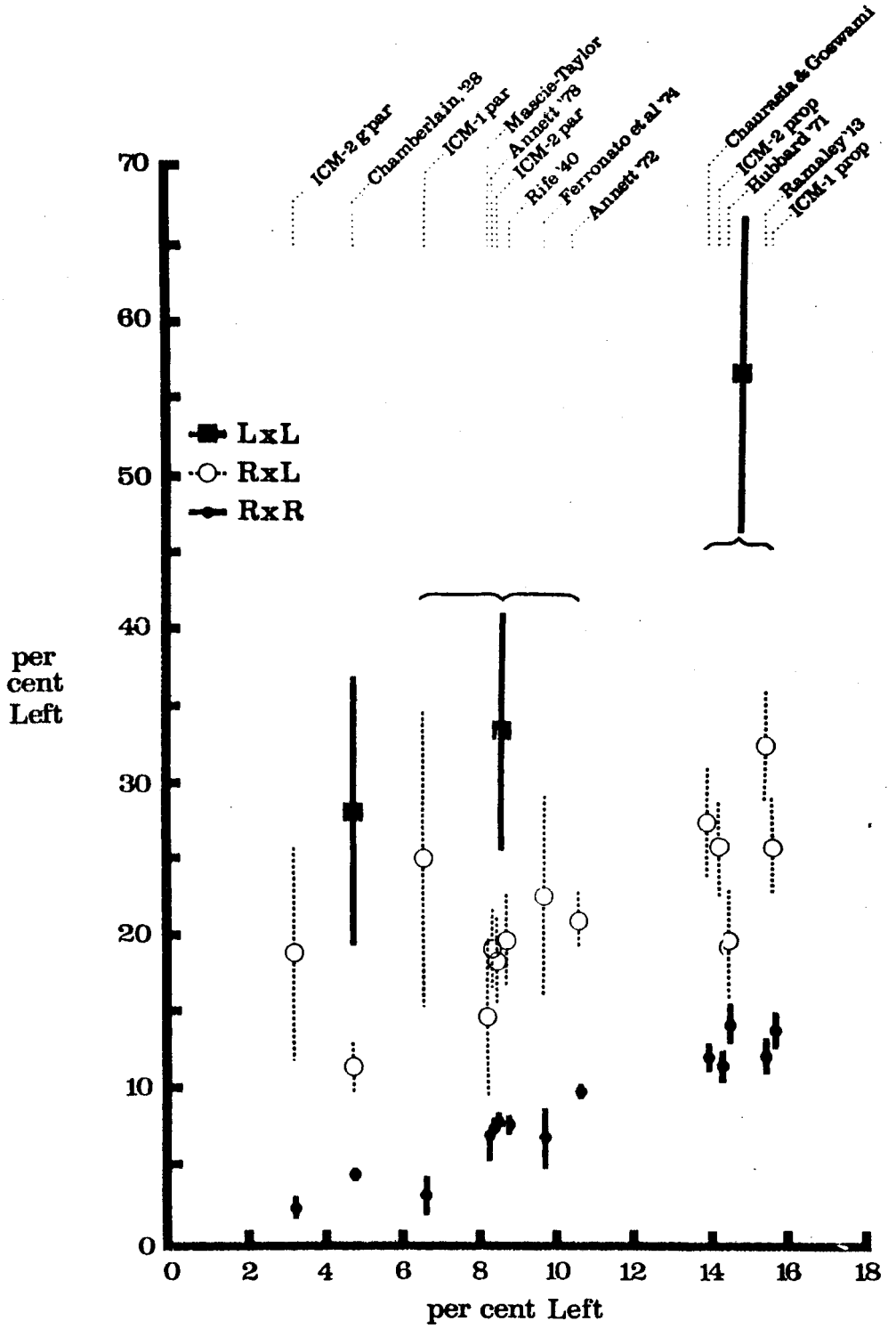

ICM-2 g'par
Chamberlain, '28
ICM-1 par
Mascie-Taylor
Annett '78
ICM-2 par
Rife '40
Ferronato et al '74
Annett '72
Chaurasia & Goswami
ICM-2 prop
Hubbard '71
Ramaley '13
ICM-1 prop
LxL
RxL
RxR
per cent Left
per cent Left
0
10
20
30
40
50
60
70
0
2
4
6
8
10
12
14
16
18

Figure 7.2 shows the goodness of fit of the Annett (1972) model to all the 14 data sets of Table 7.1, and all of the 18 MZ and 17 DZ twin data sets of Table 7.2. Figures 7.2 to 7.13 are all basically similar and have the same conventions. Figures 7.2, 7.3, 7.6, 7.8, 7.10, 7.11 and 7.13 each show six small contour maps. The upper left map (a) is for the goodness of fit of the progeny of R x R matings, the upper right map (b) is for the goodness of fit of the progeny of R x L matings and the middle left map (c) is for the goodness of fit of the progeny of L x L matings. The combined values of these three values are shown in the middle right map (d). The goodness of fit of MZ twins is shown in the lower left map (e) and the goodness of fit of the DZ twin data is shown in the lower right map (f). The combination of the MZ, DZ and Family data (i.e, maps d, e and f) is shown in Figures 7.5, 7.7, 7.9 and 7.12; it is not applicable in all cases.

The abscissa of each box represents a particular value of the degree of inheritance; in figures 7.3-12 it is the value of $p(L|DC)$, and in figures 7.2 and 7.13 it is the size of the 'right shift' (in z units). The ordinate in figures 7.3-12 is the hypothesised true incidence of left-handeness, and in figures 7.2 and 7.13 the ordinate is the proportion of individuals who are of phenotype RS-.

Within the boxes are plotted contour maps of the probability density of the goodness of fit of the particular models. In general, green contours are acceptable with $p > 0.05$ and red contours are rejected with $p < 0.05$. Green

contours are plotted at levels of 0.05, 0.10, 0.2o, 0.30, 0.40, 0.50 (thickened line), 0.60, 0.70, 0.80, and o.90, and 0.95. Red contours are plotted at levels of 0.045, 0.01, 0.005, 0.001 (thickened line), 0.0001, 0.00001, 0.000001 and 0.0000001, as well as at values of 0.955, 0.99, 0.999, 0.9999 and 0.99999 (i.e. the fit is too good).

In boxes a,b,c,e and f the red and green contours may simply be read off to show the goodness of fit of a particular model. For the combined family data (box d), and for the overall combined data (figures 7.5, 7.7, 7.9 and 7.12), the probability levels depend upon the particular number of degrees of freedom used. As explained in appendix 7.1, this is somewhat controversial. For the family and combined data I have therefore plotted two distinct sets of probability contours. The red and green contours represent the probability values stated earlier for the more <u>conservative</u> test of goodness of fit. In these boxes there is also a heavy black line, which is always outside the green area, and this represents the goodness of fit at the 0.05 level, on a more <u>liberal</u> test.

If for the combined data there is no fit both at the 0.0 level on the more liberal test, and at the 0.0000001 level on the more conservative test, then no graph is given.

For figures 7.3 to 7.7 the degrees of freedom for boxes a-f, and the combined data, are 14, 14, 3, 17 (31), 18, 17 and 52 (66) respectively, liberal tests, where relevant, being shown in brackets. For figures 7.8 to 7.12 the respective degrees of freedom are 12, 12, 3,15 (27), 17, 16 and 48 (60). For figure 7.2 the degrees of freedom are 14, 14, 9, 23 (37), 18, 17, 60 (74), and for figure 7.13 are 12, 12, 9 21(33), 17, 16 and 56 (68). The difference between the Annett and other models is that in the case of the Annett model, data sets have not been combined when the L x L values are relatively small; in consequence the estimate of the Chi-squared and the df may be slightly in error.

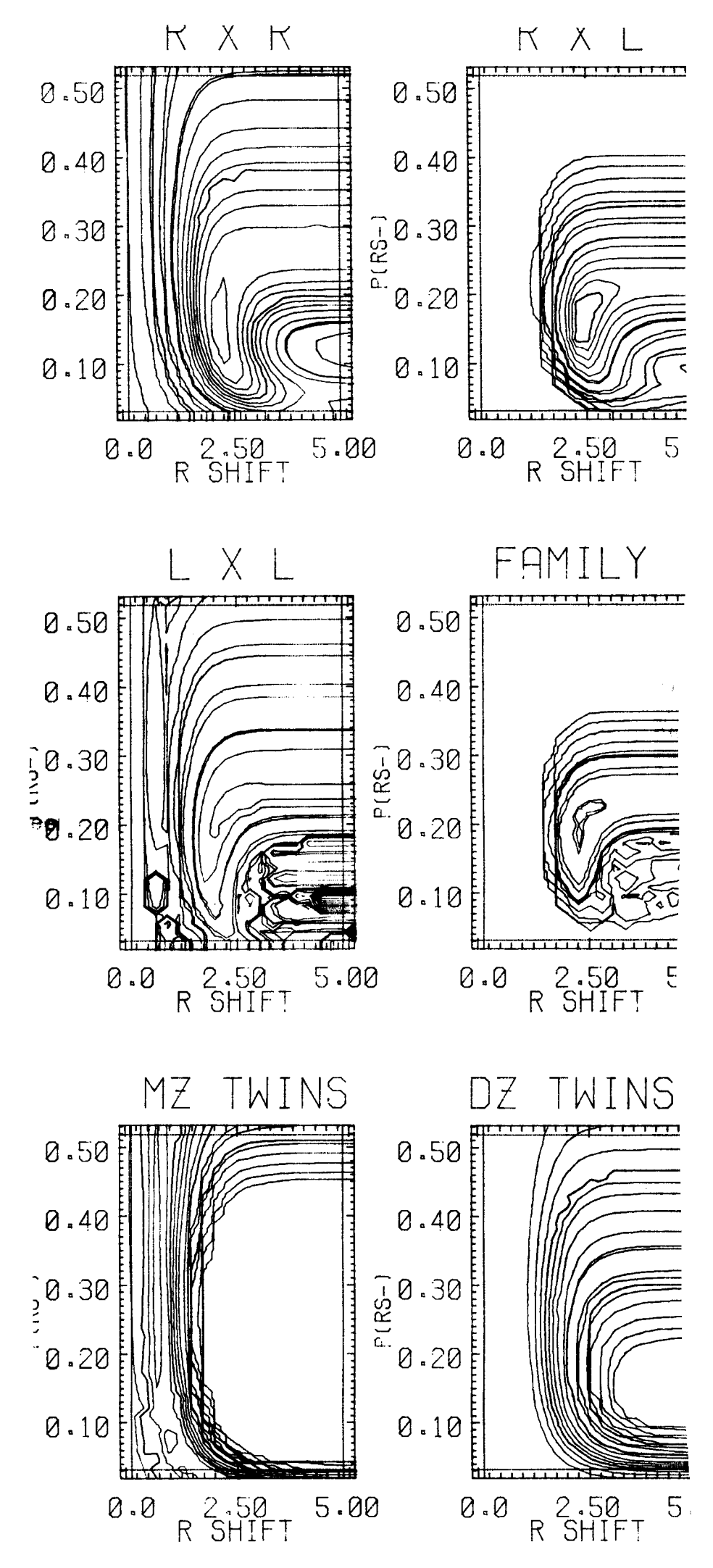

K X K
K X L
L X L
FAMILY
MZ TWINS
DZ TWINS
P(RS-)
0.50
0.40
0.30
0.20
0.10
0.0
2.50
5.00
R SHIFT

Figure 7.3 Shows the goodness of fit of the Rife model to all of the family data of Table 7.1 and to the twin data of Table 7.2. See the legend to Figure 7.2 for details.

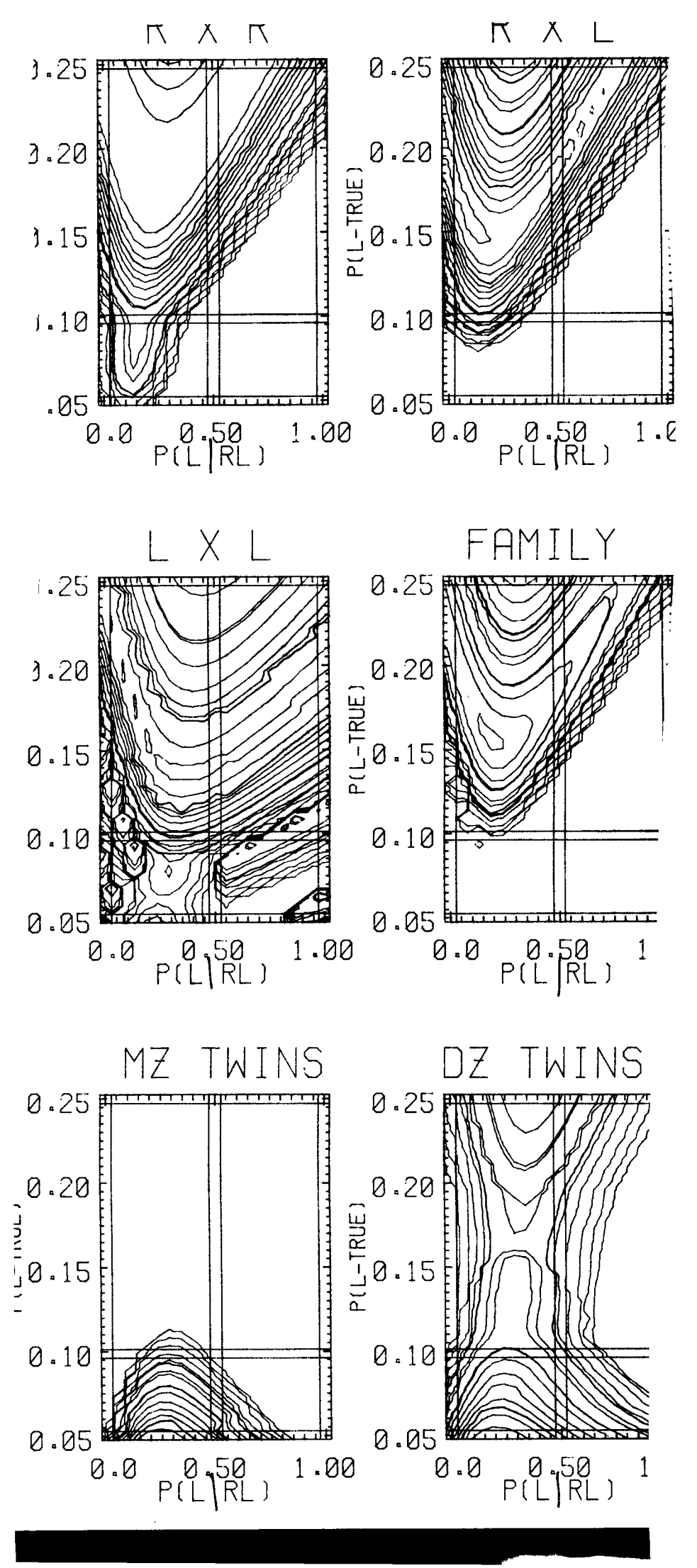

Π X Π
Π X L
L X L
FAMILY
MZ TWINS
DZ TWINS
P(L-TRUE)
P(L|RL)
0.0
0.50
1.00
0.05
0.10
0.15
0.20
0.25

Figure 7.4 Shows the goodness of fit of the Trankell model to all of the family data of Table 7.1 and the twin data of Table 7.2. See the legend to Figure 7.2 for details.

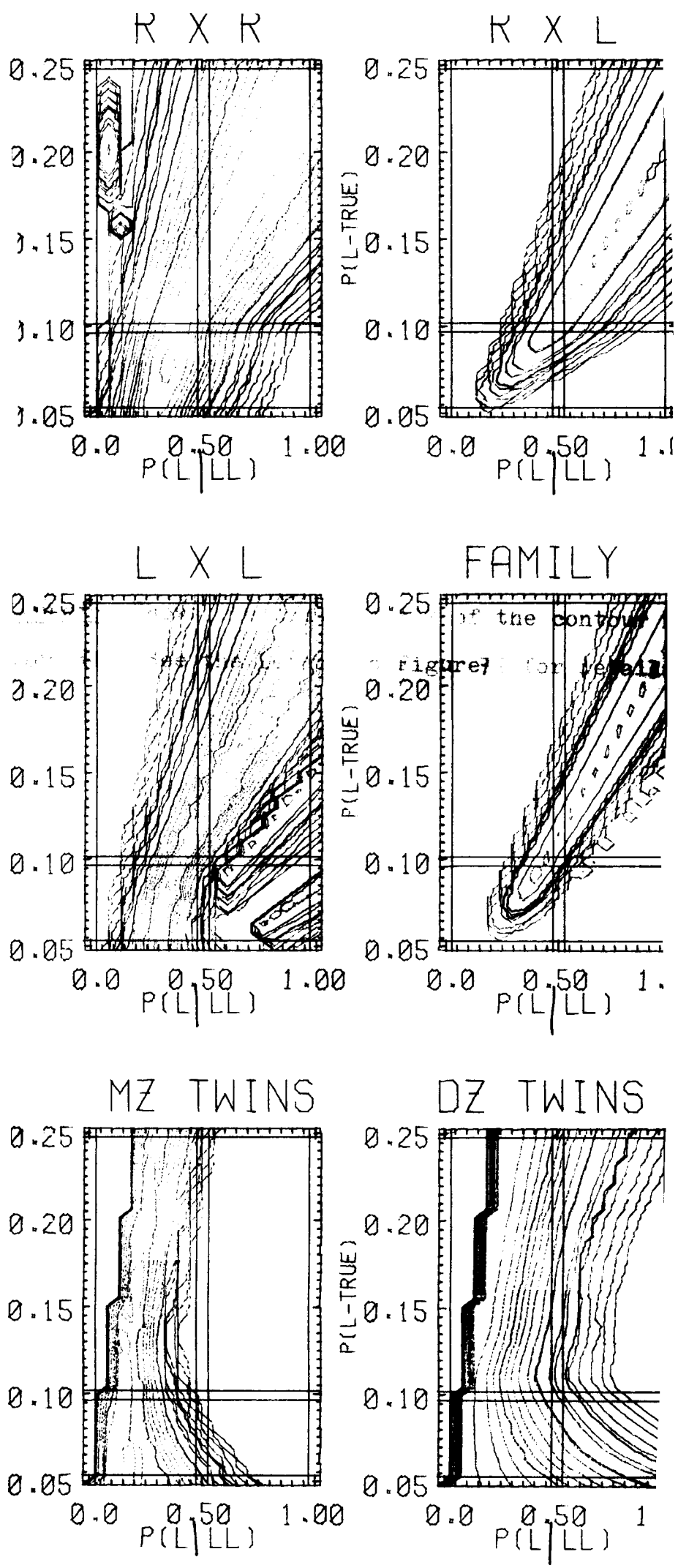

R X R
R X L
L X L
FAMILY
MZ TWINS
DZ TWINS
P(L-TRUE)
P(L|LL)
0.25
0.20
0.15
0.10
0.05
0.0
0.50
1.00

Figure 7.5 Shows the combined fit of the contour maps of Figure 7.4. See the legend to Figure 7.2 for details.

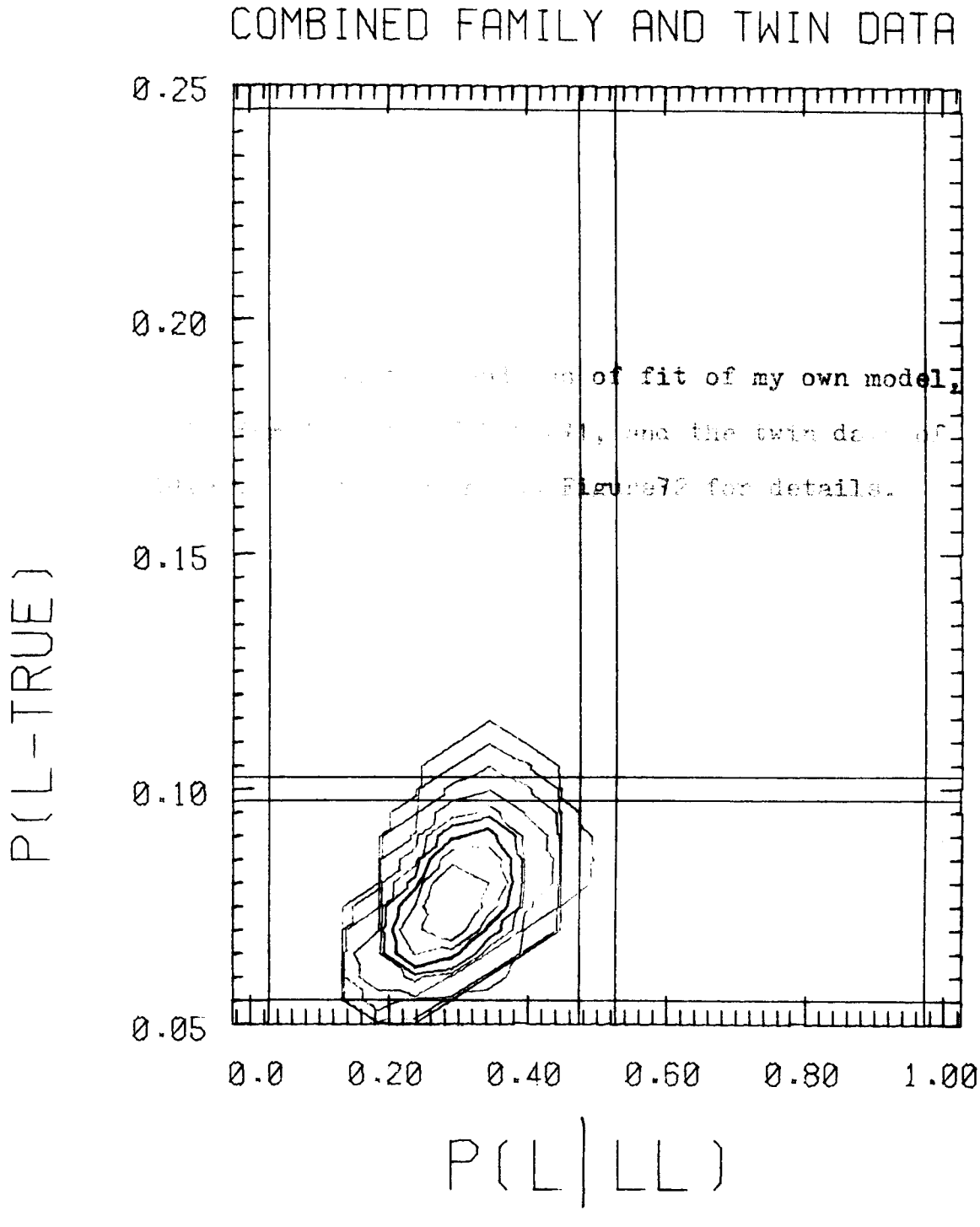

COMBINED FAMILY AND TWIN DATA
0.25
0.20
0.15
0.10
0.05
P(L-TRUE)
0.0
0.20
0.40
0.60
0.80
1.00
P(L|LL)

Figure7.6 Shows the goodness of fit of my own model, to the family data of Table7.1, and the twin data of Table7.2. Se the legend to Figure7.2 for details.

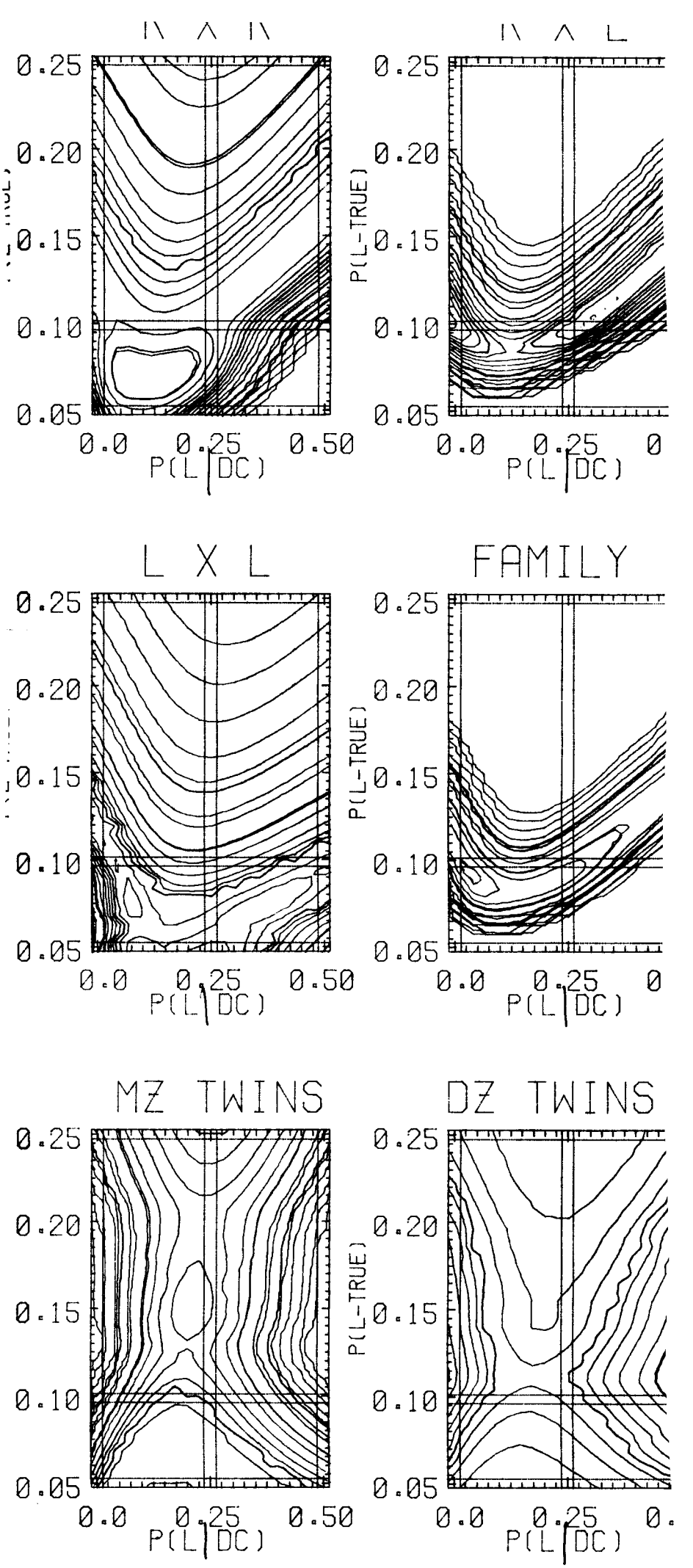

N A N
N A L
L X L
FAMILY
MZ TWINS
DZ TWINS
P(L-TRUE)
P(L|DC)
0.25
0.20
0.15
0.10
0.05
0.0
0.50

Figure 7.7 Shows the combined fit of the contour maps of Figure 7.6. See the legend to Figure 7.2 for details.

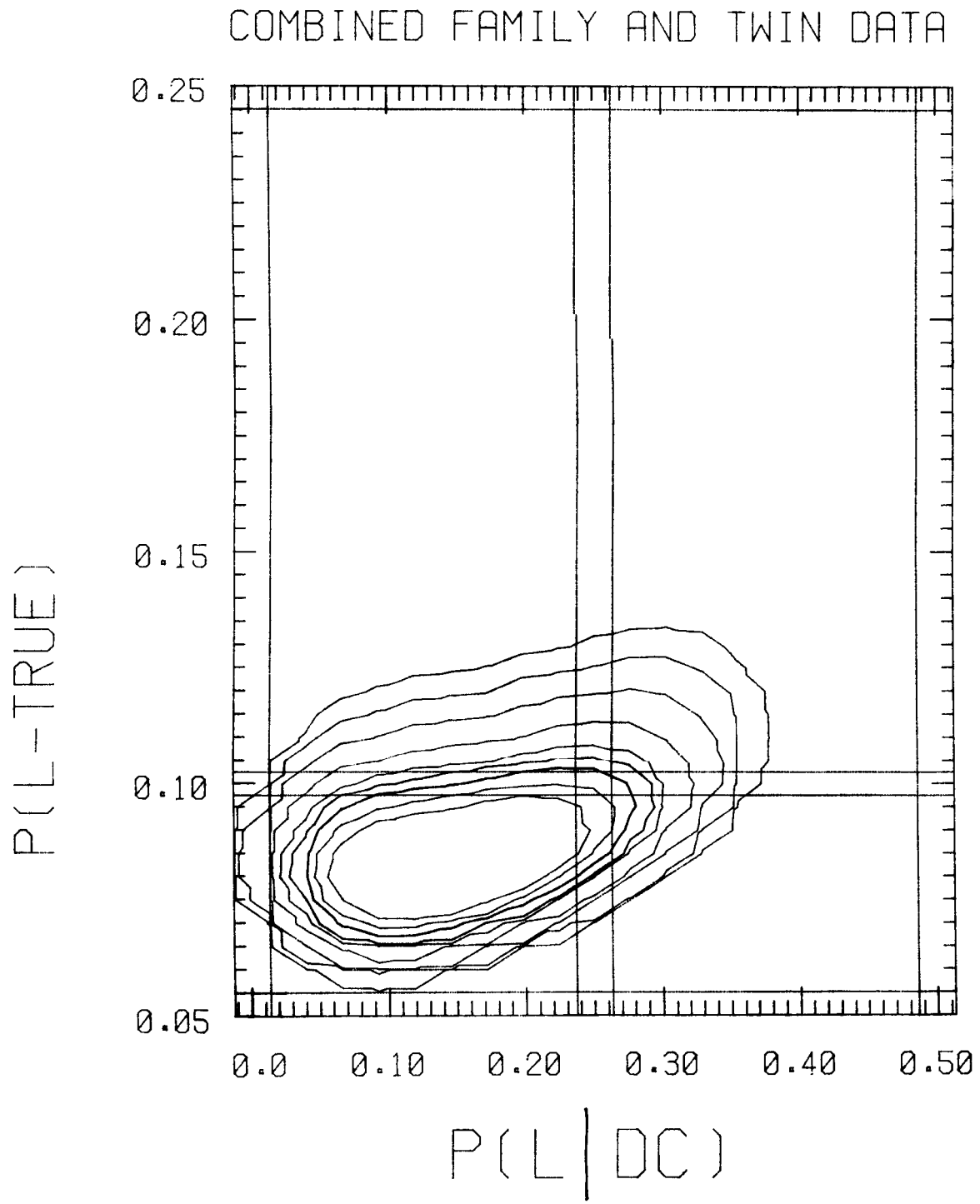
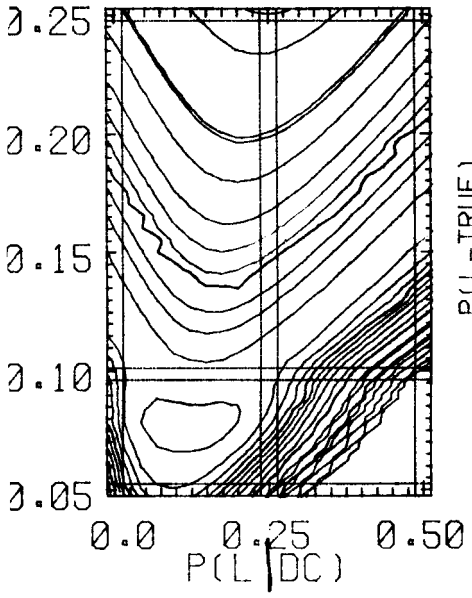
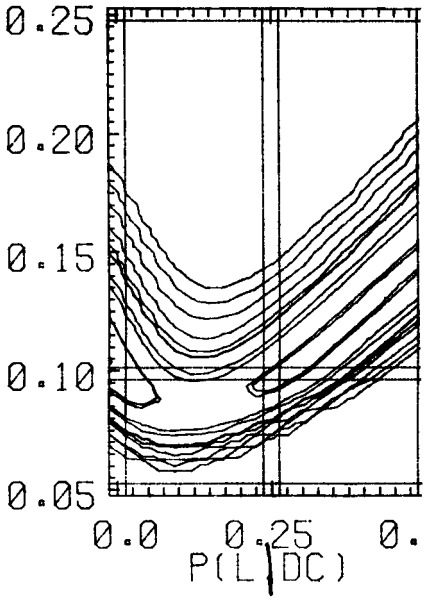
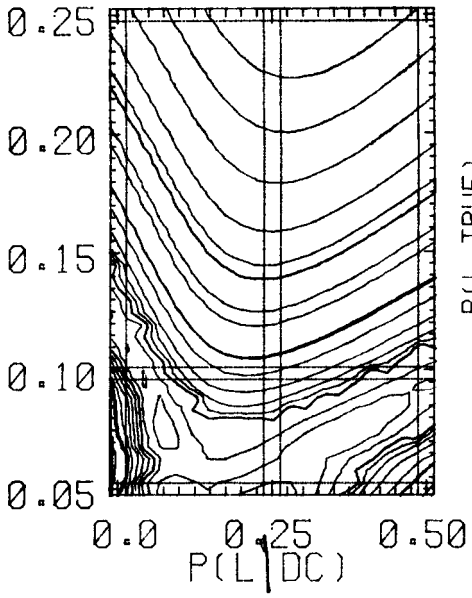

COMBINED FAMILY AND TWIN DATA
0.25
0.20
0.15
0.10
0.05
P(L-TRUE)
0.0
0.10
0.20
0.30
0.40
0.50
P(L|DC)

Figure 18 Shows the goodness of fit of my own model to a slightly restricted set of family data and twin data (see text). See the legend to Figure 12 for details.

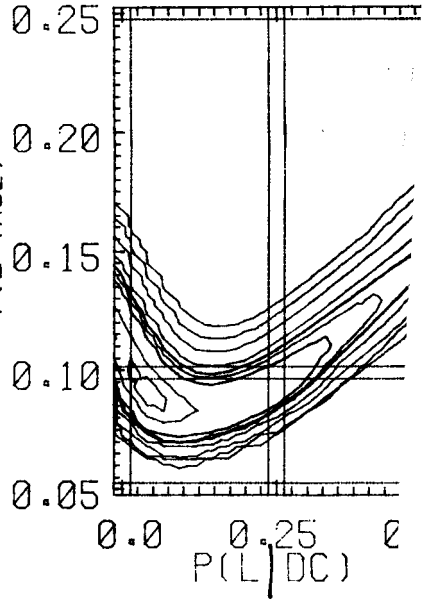




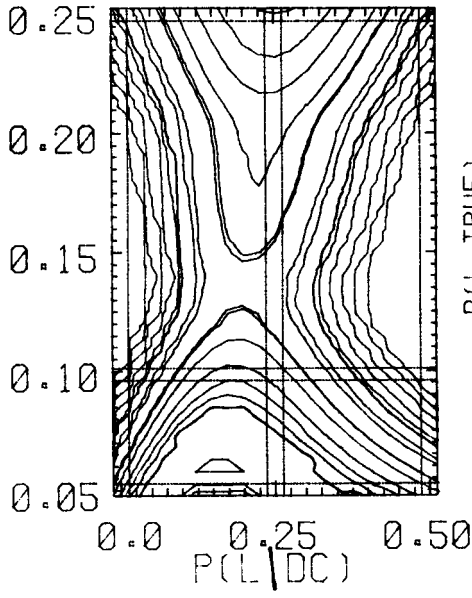
L X L



FAMILY



MZ TWINS



DZ TWINS

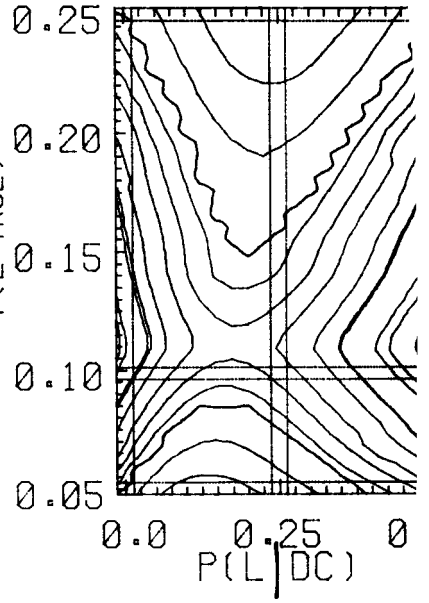


Figure 7.9 Shows the combined fit of the contour maps of Figure 7.8. See the legend to Figure 7.2 for details.

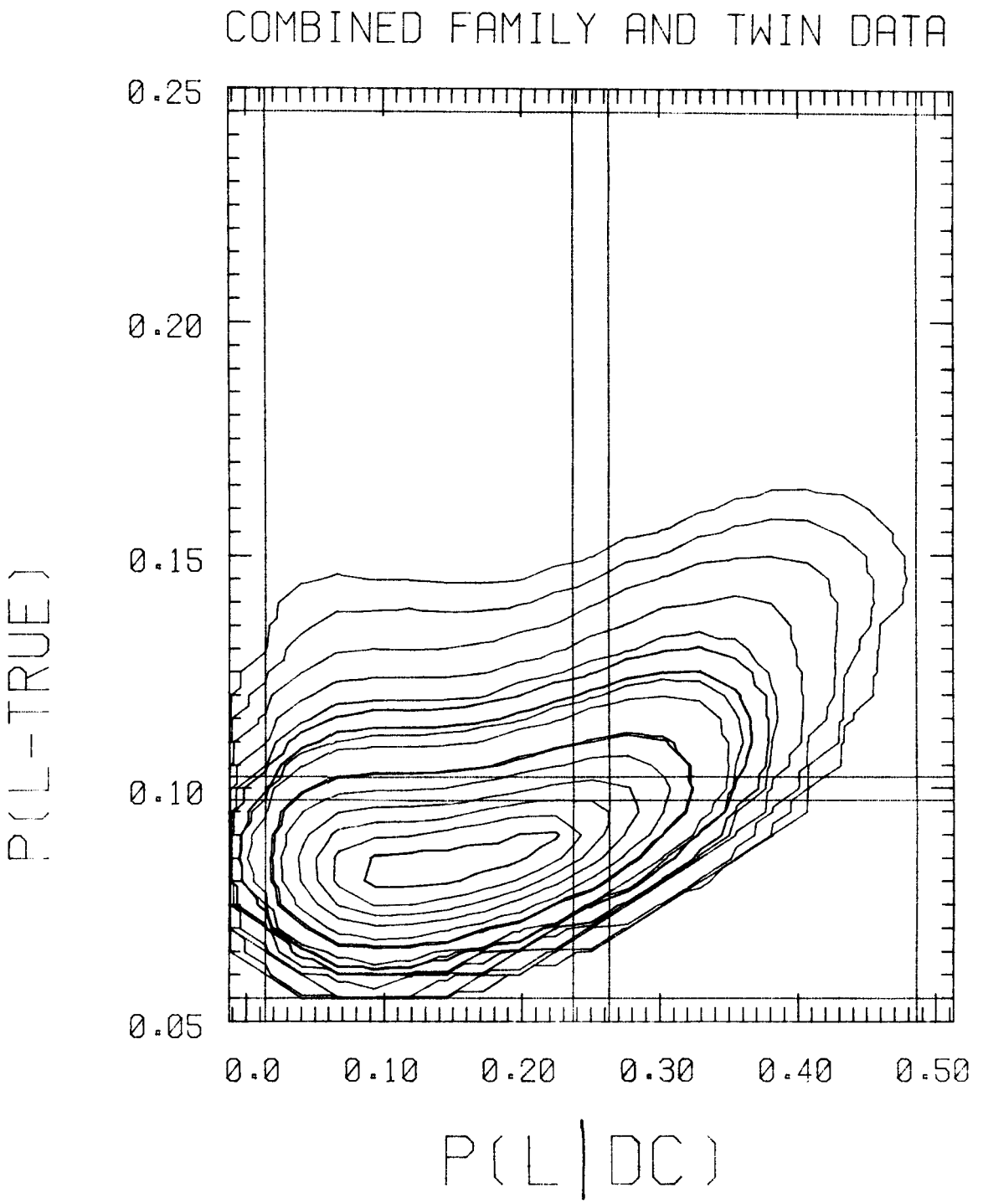
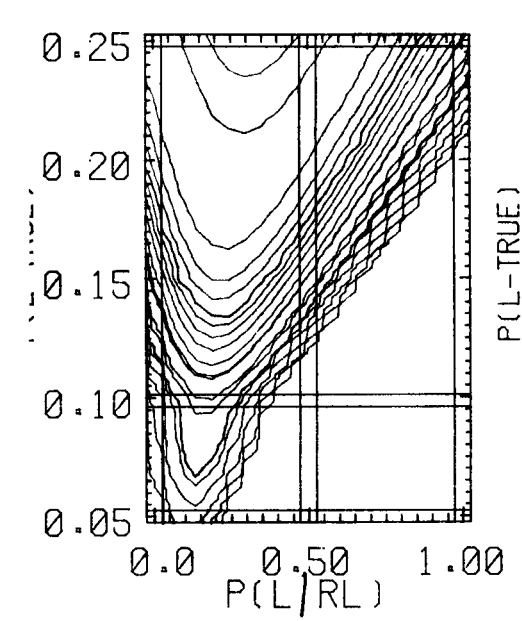
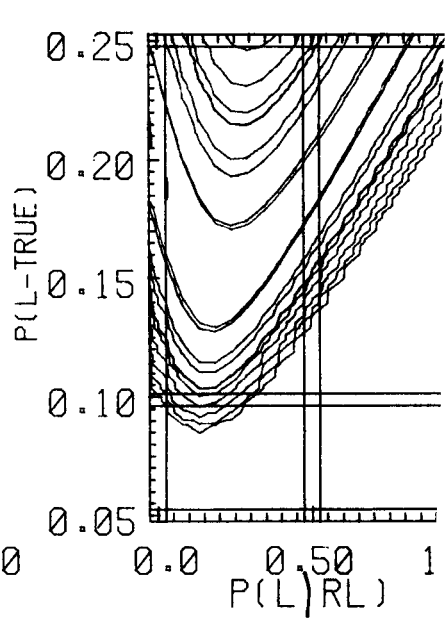
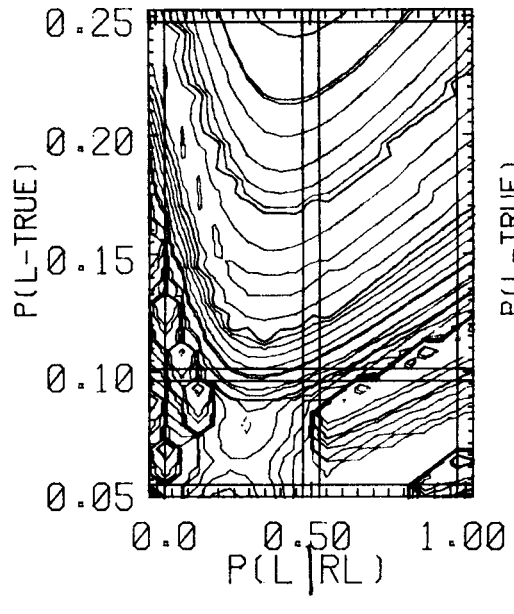

COMBINED FAMILY AND TWIN DATA
0.25
0.20
0.15
0.10
0.05
P(L-TRUE)
0.0
0.10
0.20
0.30
0.40
0.50
P(L|DC)

Figure7.10 Shows the goodness of fit of the Rife model to the restricted set of family and twin data (see text). See the legend to Figure7.2 for details.

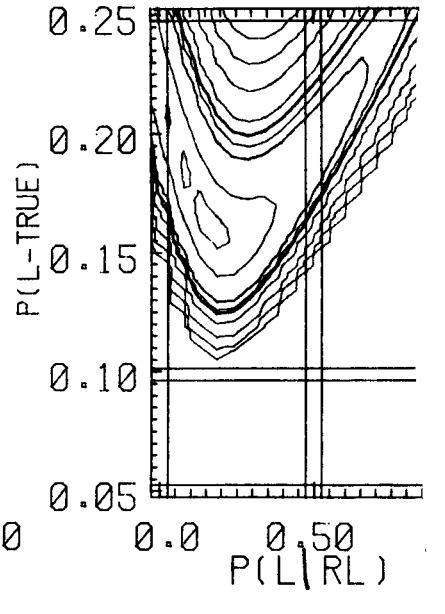




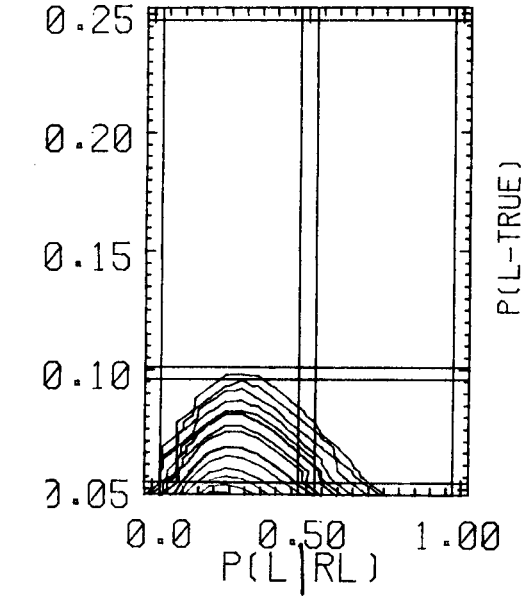
L X L



FAMILY



MZ TWINS



DZ TWINS

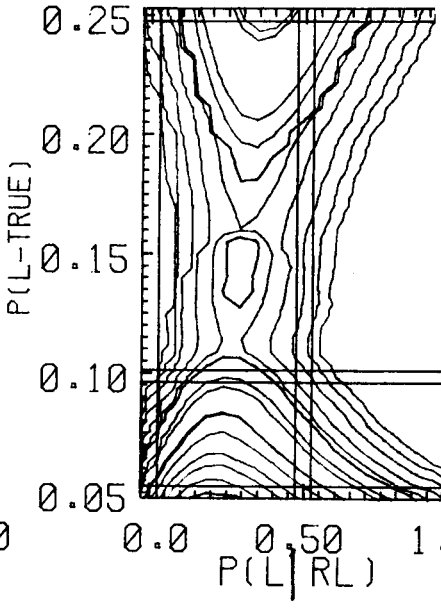
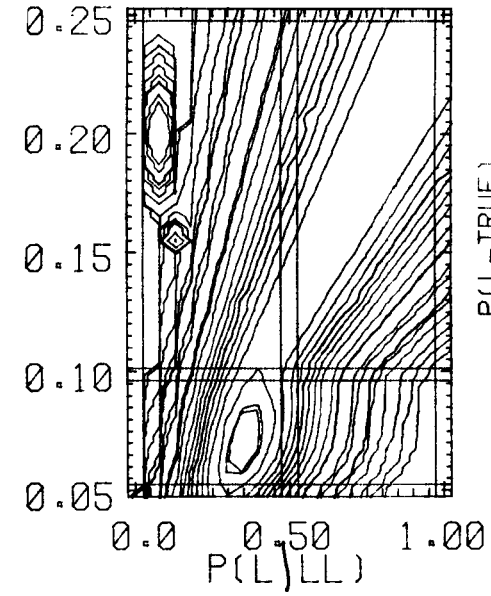
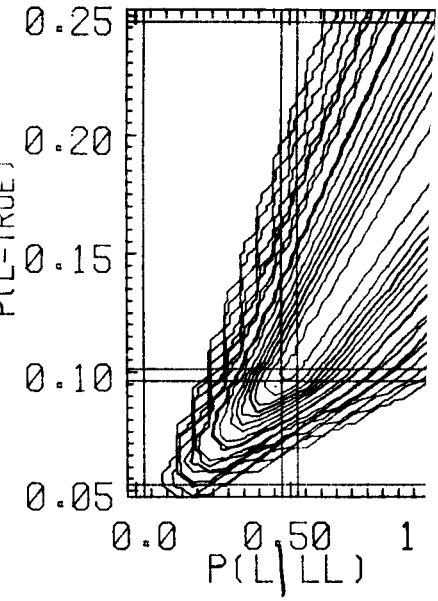
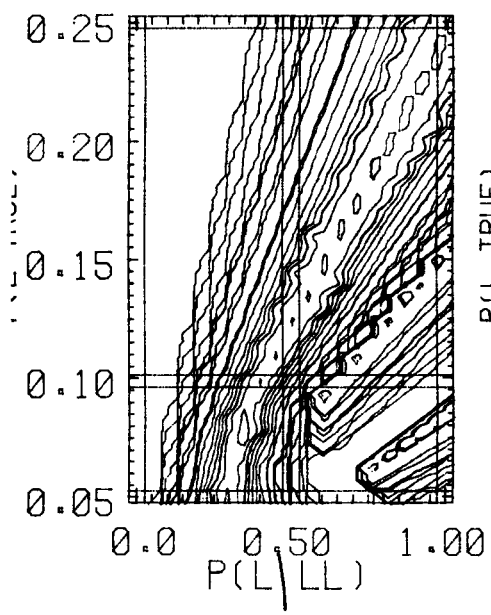


Figure7.11 Shows the goodness of fit of the Trankell model to the restricted set of family and twin data (see text). See the legend to Figure7.2 for details.

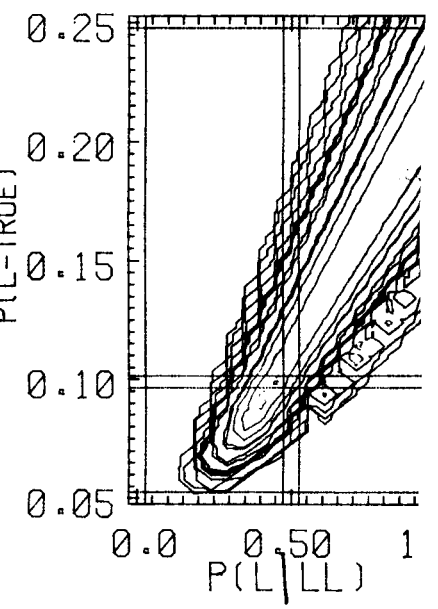




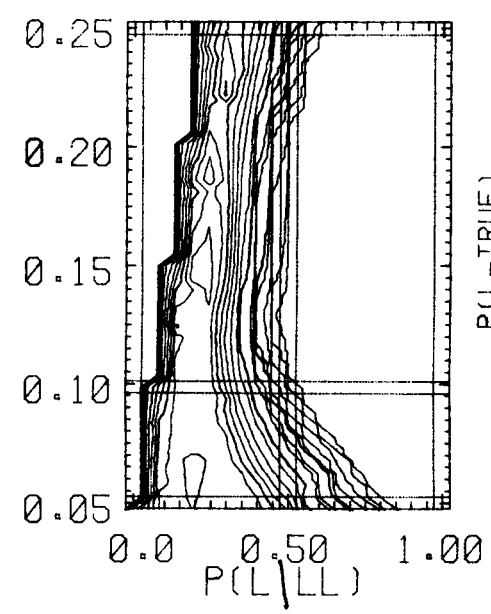
L X L



FAMILY



MZ TWINS



DZ TWINS

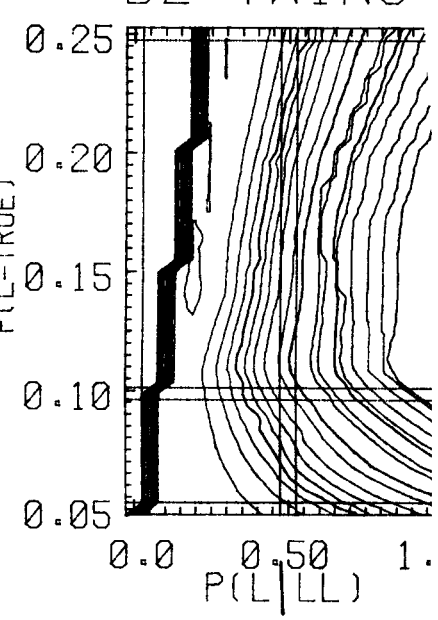


Figure 7.12 Shows the combined fit of the contour maps of Figure 7.11. See the legend to Figure 7.2 for details.

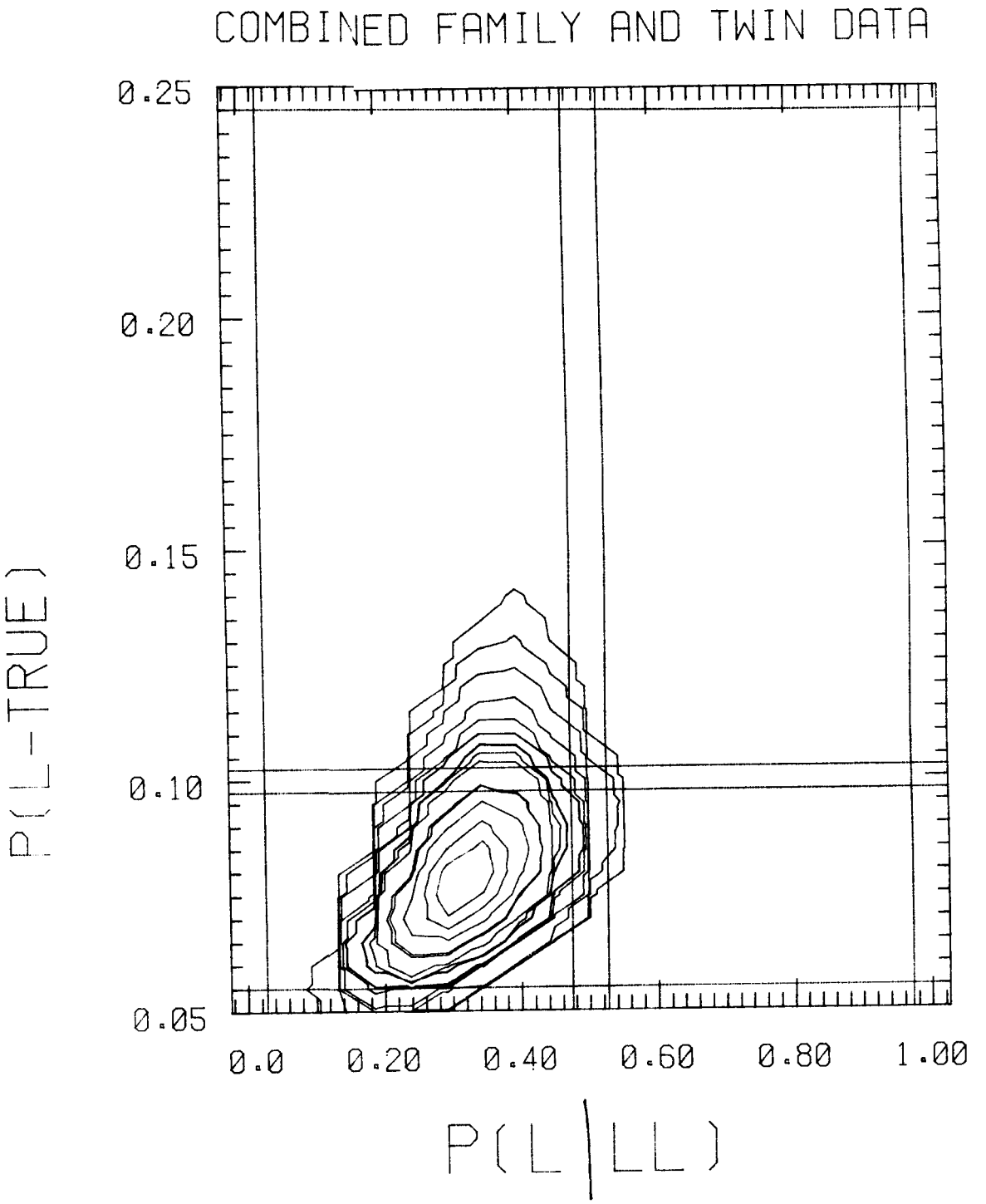
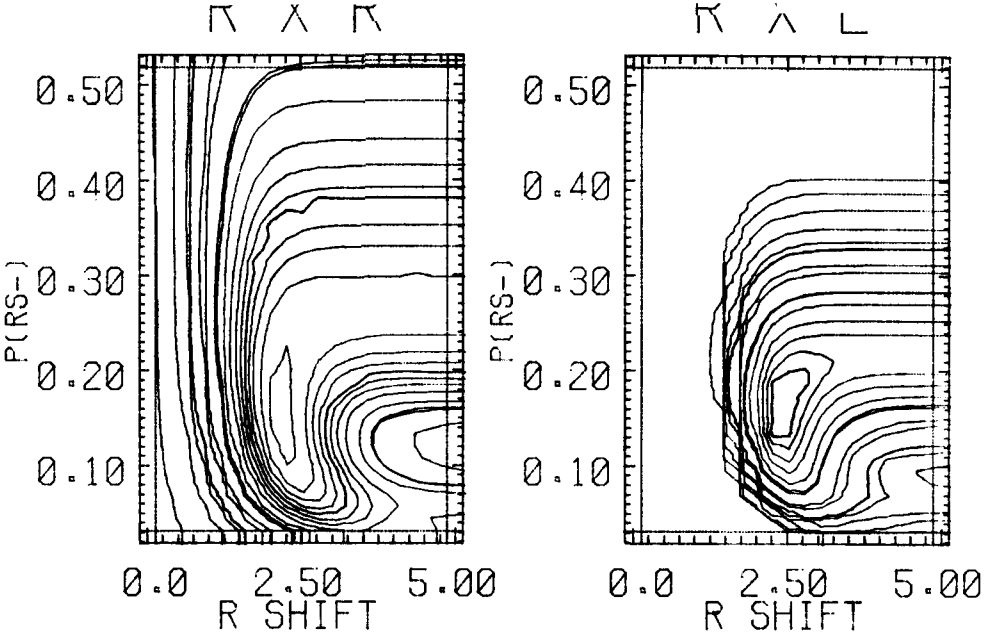
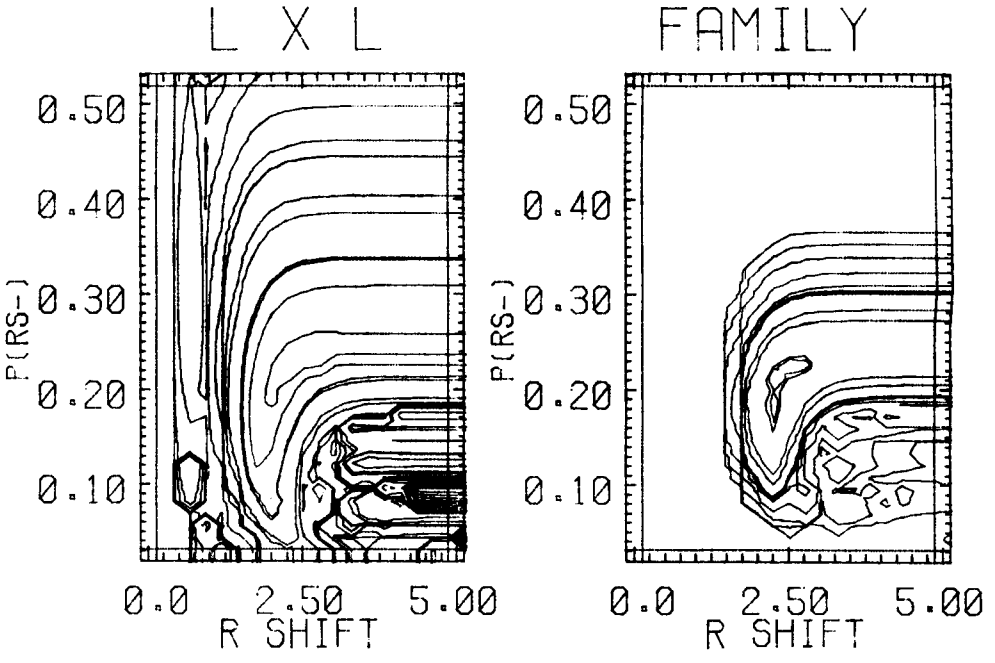

COMBINED FAMILY AND TWIN DATA
0.25
0.20
0.15
0.10
0.05
P(L-TRUE)
0.0
0.20
0.40
0.60
0.80
1.00
P(L|LL)

Figure 7.13 Shows the goodness of fit of the Annett model to the restricted set of family and twin data (see text). See the legend to Figure 7.2 for details.


R X R
R X L
0.50
0.40
0.30
0.20
0.10
P(RS-)
0.0
2.50
5.00
R SHIFT


L X L
FAMILY
0.50
0.40
0.30
0.20
0.10
P(RS-)
0.0
2.50
5.00
R SHIFT

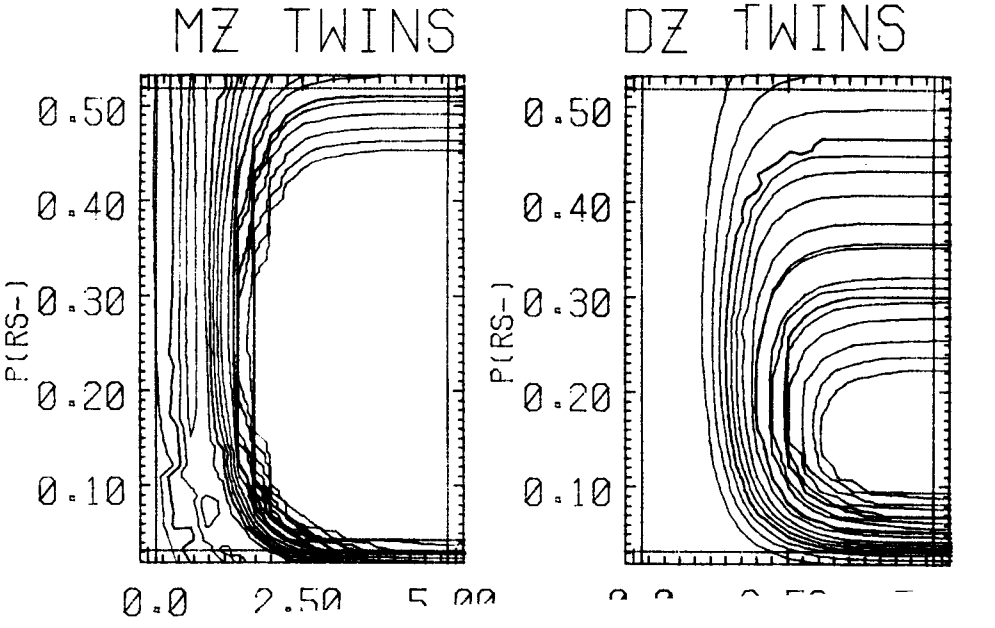
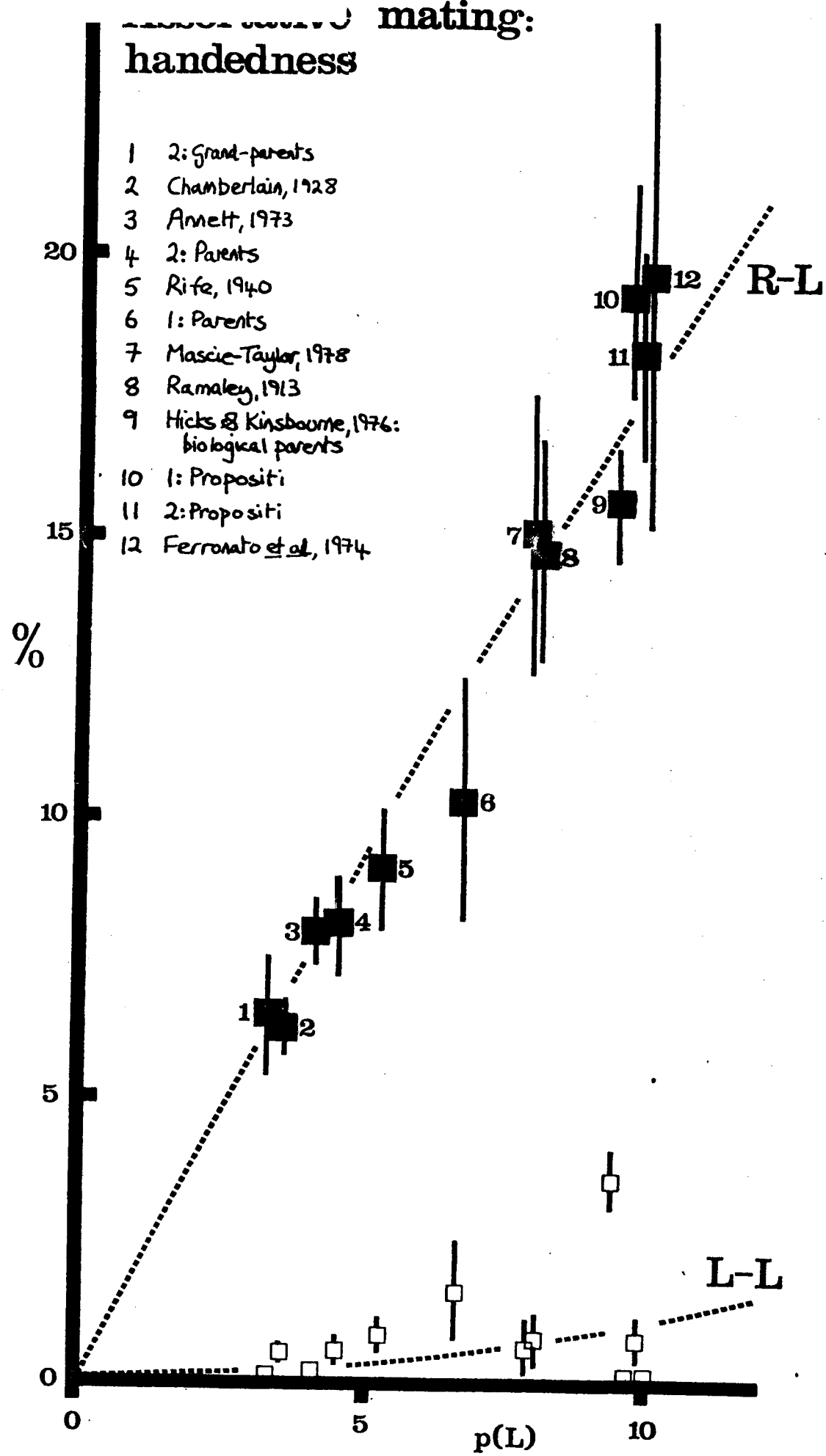

MZ TWINS
DZ TWINS
0.50
0.40
0.30
0.20
0.10
P(RS-)
0.0
2.50

Figure 7.14 Shows the proportion of R-L and L-L matings in different studies as a function of the overall incidence of left-handedness in that particular generation. The step-parent data of Hicks and Kinsbourne (1976) have been omitted as p(L) is exceptionally high at 31.9%.


mating:
handedness
1 2: Grand-parents
2 Chamberlain, 1928
3 Arnett, 1973
4 2: Parents
5 Rife, 1940
6 1: Parents
7 Mascie-Taylor, 1978
8 Ramaley, 1913
9 Hicks & Kinsbourne, 1976: biological parents
10 1: Propositi
11 2: Propositi
12 Ferronato et al, 1974
R-L
L-L
%
20
15
10
5
0
0
5
10
p(L)