6 The Genetics of Dyslexia

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Never yet was one man gifted with all graces. (I, 10)

What a wonderful thing it is that that drop of seed, from which we are produced, bears in itself the impressions, not only of the bodily shape, but of the thoughts and inclinations of our fathers. (II, 37)

Montaigne, Essays.

Introduction

Reading is a skill of central importance in a modern technological society; although to say that seems almost superfluous in a series of closely printed, densely argued volumes such as these, in which few authors or editors will do anything but take for granted that their readers have the ability to read well and quickly. However Rutter and Yule (1975) estimated that 4% of the population has specific problems with reading, and other workers have estimated prevalence rates two and three times that percentage: Tarnopol and Tarnopol (1981) estimated a median prevalence rate of 7%. Needless to say such a disability results in much personal anguish for the sufferers and their families, and potentially results in a large cost to society, particularly since many of those with dyslexia have otherwise high intellectual abilities. In quoting such figures it should be emphasized that we are only considering individuals with developmental dyslexia; the separate but rare condition of acquired adult dyslexia will not be considered in this chapter except where otherwise stated.

Variation in any biological or psychological characteristic always means that questions are asked about the causes of the variation, and the two broad classes of explanation invariably reduce to environmental and genetic factors, or their interaction. The first description of dyslexia as a specific syndrome is usually credited to Morgan (1896) although Finucci (1978) has pointed out that Kerr (1897)

actually published an earlier description of congenital cases (acquired cases of 'word blindness' being well known at that time, e.g. Hinshelwood, 1895). Within a decade or so of Morgan's description (see below) families were being described in which there were multiple affected members, and the possibility of an inherited tendency was being raised. The attraction of genetic theories is somewhat surprising at first sight since reading, unlike many physiological or psychological processes, is so obviously acquired from the environment: reading and writing are necessarily cultural processes, with their arbitrary structure of abstract written letters which differ between societies; they have arisen very recently in human evolution, within the last five millenia or so; and they are so obviously acquired as a result of education extending through a long and important period of a child's life. The attraction of genetic theories is, like so many deeper reasons behind supposedly rational scientific theories, strongly over-determined. Some of the reasons are biological, and will be considered below; but other reasons undoubtedly reflect the need for individuals to explain and excuse their own and other's inability to carry out what is superficially a trivial task, and to account for the absence of causal explanations which can otherwise account for one individual in a family showing problems in the absence of parental support and good teaching. For these reasons it is necessary to examine critically the claim that dyslexia has a genetic basis, and to tease apart the strengths and weaknesses of that hypothesis.

Biological Correlates of Dyslexia

Dyslexia shows a number of characteristics which are broadly called 'biological', and for which the implication is that since it is difficult to explain them in terms of social and other environmental processes, that they must therefore be the result of genetic processes. The sex difference is the outstanding biological characteristic, and will be considered first. In so doing one must avoid the naive fallacy that a different incidence between the sexes implies a biological origin for characters. For example, the excess of men over women in professions such as medicine cannot be construed as the direct effect of some hypothetical gene for medical practice; instead it probably reflects the indirect genetic effects of phenotypic external sexual characteristics determining cultural processes. This hypothesis is supported by the recent rapid change in the proportion of female entrants to medical school (McManus, 1982; McManus *et al.*, 1989).

Sex Differences

Critchley (1970) cites nineteen studies of dyslexia, involving a total of 2986 children, of whom 76.7% were male, a ratio of 3.29 males to each female. (It is interesting, in passing, to note that he omitted from his summary table the study of Jastak (1934) in which no difference was found.) The sex-ratio which Critchley reported is undoubtedly a typical estimate of many studies; other examples being 76.7% males (Rutter and Yule, 1975), and 76.8% males (DeFries and Decker, 1982). The excess of males with dyslexia is mirrored by the generally superior performance of females on tests of verbal ability, estimated at about 0.25 standard deviations (Maccoby and Jacklin, 1975) or 0.11 standard deviations (Hyde and Linn, 1988). A female advantage is also seen in tests of reading as well as of vocalization. But reading and verbal abilities are generally highly correlated. McManus and Mascie-Taylor (1983) have analysed data from the large National Child Development Study, considering the specific variance in verbal, non-verbal and reading tests which is not explained by variation in the other tests. They showed that girls at age 11 actually perform less well on the reading test than do boys, as they also do on the non-verbal test. But their greatly superior performance on the verbal test means that when raw reading scores are considered overall they perform better than do boys. The implication is that girls are better at reading in so far as it contains a large verbal component; but that they are not necessarily better on the specific component which is unique to reading.

Taken overall, however, there seems to be little doubt that males are less good at reading than are females, and that they suffer a higher rate of dyslexia. However, as Satz and Zaide (1983) have asked, does that constitute an aetiological clue or merely perpetuate a myth?

Neurobiological Correlates

Morgan (1896) speculated that congenital word blindness might be due to a 'defective development of that region of the brain ... which in adults produces practically the same symptoms[,] ... the left angular gyrus'. Likewise Hinshelwood (1900) speculated on the role of the angular and supramarginal gyri, and Clairborne (1906) suggested that there may be an imperfect development of the angular gyrus. Since that time there have been many attempts to find neuropathological changes underlying dyslexia. Such studies are not easy however because of the rarity of cases which come to post-mortem and in which the brain is examined systematically. The first clear case of dyslexia to be examined properly was a 12-year-old boy reported by Drake (1968); he reported thickened cerebral cortex in the parietal area, with ectopic neurones in the white matter. A second patient reported by Galaburda and Kemper (1979), Galaburda (1982) and Galaburda and Eidelberg (1982) was 20 years old at the time of death, and showed micropolygyria in the posterior superior temporal gyrus and focal cortical dysplasia, coupled with thickening of the white matter in the left hemisphere; the right hemisphere was almost normal. In addition there were bilateral thalamic abnormalities. Galaburda (1983) has speculated that these defects reflect a defect of cellular migration, which 'might reflect a genetic defect in the cellular programming of neuronal migration' (and indeed neuronal migration is partly under genetic control – see Nowakowski, 1986). Galaburda *et al.* (1985) have reported a further case of a 19-year-old dyslexic who showed multiple dysplasias and ectopias which affected the cortex of both cerebral hemispheres but seemed particularly to affect the left superior temporal gyrus and left inferior frontal gyrus. In reviewing these cases Galaburda (1986) has pointed out that ectopia and dysplasia imply an early onset during fetal development, and therefore exclude as causal factors traumatic or other environmental insults in the perinatal period or later. That indeed neuronal migration is the principal mechanism for the ectopias and dysplasias is suggested by animal work in which similar lesions can be induced in neonatal rats (Dvorak and Feit, 1977; Dvorak *et al.*, 1978). Sherman *et al.* (1989) have developed the analogy between the lesions found in dyslexia and in experimental rats and mice, and have argued that they could form a model for dyslexia in humans.

At a gross morphological level, Hier *et al.* (1978) compared computerized tomographic scans of the brains of 24 dyslexics and controls and found no structural abnormalities, although there was evidence of a reversal of the normal pattern of asymmetry in 10 of the cases. Rosenberger and Hier (1980) also found reversed cerebral asymmetry in children with verbal learning difficulties.

Abnormalities of the EEG in dyslexics have been exten-

sively studied (see Pirozzolo and Hansch, 1982 for a review); taken overall there is probably evidence for an increased rate of electroencephalographic abnormalities in dyslexic children.

As yet there seem to have been no studies of dyslexics using the newer techniques of functional brain mapping (see Wood and Felton, 1983 for a review), although recent work using positron emission tomography (Petersen *et al.*, 1988) would suggest that soon there could be exciting results which would help to delineate areas of functional abnormality in dyslexics.

Summarizing the studies on structural and functional abnormalities in dyslexia, there would seem to be good *prima facie* evidence for abnormalities at the cytological level, which may well represent abnormalities of early development, although Hynd and Semrud-Clikeman (1989) have emphasized that there are many inconsistencies of detail between the findings. The problem in interpreting the data is that so few dyslexic brains have been studied, and hence there is a real risk of reporting biasses due to only abnormal brains being described. If dyslexia is truly present in 5% or more of the population then it should also be present in 5% of the population coming to post-mortem, including those in the age-range of 10 to 30, in whom acquired cerebral disease is unlikely. Death at that age is rare but not so rare as to make a properly controlled study impossible. Thus to take some very crude estimates, based on UK population forecasts (Social Trends, 1975), the extrapolated population of UK males for 1991 under the age of 30 is 13.2 million. The death rate for accidents of all sort in males of this age-range is approximately 33/100 000 per annum, meaning that about 4400 males will die in each year; of these about 5% may be expected to have dyslexia, giving a total of about 220 cases per annum reaching post-mortem. In the USA the figures will be approximately four times larger. In all accident cases the coroner will order a post-mortem, and the brain will be available for histology. When compared with such numbers the number of cases being reported in the literature is absurdly small, and surely insufficient for making any large-scale conclusion.

Finally it must be noted that merely because structural abnormalities are present during fetal development this does not imply a genetic causation (as Galaburda (e.g. 1983) in particular has implied); the fallacy can be seen by considering the parallel between cortical dysplasia in dyslexia and the logically equivalent case of a condition such as phocomelia, which eventually was shown to be due to the environmental influence of the drug thalidomide. Indeed the parallel is closer; in more recent work Galaburda (1986) has followed up the work of Layton and Hallesey (1965), which showed that asymmetric limb defects in rats could be induced by administration of acetazolamide. Galaburda found that the drug also induces cortical abnormalities due to arrested neuronal migration.

In summary, dyslexia may well be associated with specific neuropathological defects; but that fact alone says nothing about the genetic or environmental origin of the condition.

Left-Handedness and Atypical Cerebral Lateralization

Orton (1925) was one of the first to emphasize that there seemed to be an excess of left-handers in dyslexics and in their families. He was following a tradition which suggested that abnormal lateralization and posture were responsible for many defects of reading and writing (Gould, 1905). Since that time there have been many studies that have suggested a raised incidence of left-handedness in dyslexia (e.g. Annett and Kilshaw (1984) in which 18.6% of 129 dyslexics used the left hand for writing, compared with 8.2% of 1480 normal controls), but others (e.g. McManus and Mascie-Taylor, 1983, using National Child Development Study data) have found no association between hand preference and specific reading disability. The overall association between handedness and dyslexia has been reviewed by several authors. Bryden (1982) cited Hardyck and Petrinovich's (1977) review as offering little evidence for an association; Bradshaw and Nettleton (1983) cited the review of Hicks and Kinsbourne (1976) which found five studies showing an association and three showing no association; Corballis (1983) cited the reviews of Vernon (1960) and Benton (1975) as finding little evidence for an association; Beaton (1985) reported the literature as 'thoroughly confused', emphasized the heterogeneity of the studies, but quoted Benton's (1975) conclusion that 'many of (the) essentially negative studies . . . do find a weak trend in the direction of a higher frequency of deviant lateral organisation in poor readers'; and Porac and Coren (1977) asked if there was any 'coherent way to summarise the empirical relationship between lateral preference and reading performance' and concluded that 'samples of poor readers are *never* found to be more dextral, more consistent or more congruent in their lateral preference patterns than average or good readers. Thus the literature suggests, although ambiguously, that shifts away from consistent and congruent dextrality can be associated with reading impairment' (p. 149; their emphasis). That would seem to be as fair a summary as is possible in the present situation: a verdict of 'Not Proven', as would be allowed under Scots Law.

Similarity to Other Developmental Syndromes

Childhood autism, stuttering, dyslexia, attention deficit disorder (hyperactivity) and Gilles de la Tourette's syn-

drome can all be broadly classified as developmental learning disorders, and each seems to show the same pattern of a male preponderance, an association with left-handedness and a tendency to run in families. There is good evidence in autism, stuttering and Tourette's syndrome of genetic processes (see Folstein and Rutter, 1977; Howie, 1981; Kidd, 1983; Ludlow and Cooper, 1983; Spence et al., 1985; Pennington and Smith, 1988) and in the case of autism there is suggestive evidence for neurobiological correlates (Gillberg, 1988). Taken together these features have been argued, without it must be admitted the compelling force of logic, to reflect an underlying similarity between the conditions. So dyslexia, which particularly interests us here, may have a biological basis and a genetic component.

Phenotypes of Dyslexia

The Need for Phenotypes

Genetic theory classically distinguishes between the phenotype, the way that an organism is actually observed to be, and the genotype – the genetic material carried by the organism, and which is responsible, in conjunction with environmental or other factors, for the development of the phenotype. Until a decade or two ago the genotype was at best a 'latent construct', a theoretical hypothesis of an unmeasurable, directly unknowable, internal state. With the new molecular genetics that distinction has become less important, and genotypes may now be observed directly. Nevertheless the classic corollary of the distinction, that before one could carry out genetics one had to carry out phenotypics, is still as true as ever in the first decades of the molecular genetic revolution (and may well remain so). Unless phenotypes are accurately described in a way that is biologically sensible, then genetic models will always be flawed. To take an example, it would have been difficult to have developed any sensible genetic model for the subset of mentally retarded children which have blonde hair, but once the phenotype was redefined in terms of an excess of phenylketones in the urine then the genetics of phenylketonuria could rapidly be established. With the programme for sequencing the entire human genome beginning to be developed it could be argued that the need for accurate phenotyping will be relegated to history. But that will not be for many years; and even then we will still need to know the phenotypes produced by our sequenced genotypes in order to understand the biology and the psychology of the genes we are discovering. Until that day we will be in the Catch 22 of an infinite regress: in order to find genes we will need to know phenotypes, but we can only know if our phenotypes are correct if they are predictable from genetic models.

What is Dyslexia?

An adequate phenotypic description should describe an entity (or entities) that is reliably distinguishable from other conditions, but that does not lump together conditions that are in fact separate. In historiography the distinction has been made between 'lumpers' (who look for small numbers of underlying processes) and 'splitters' (who continually differentiate between finer and finer categories). The same tendency can be found in research into dyslexia (e.g. Denckla, 1972). At one extreme are the lumpers, who argue for a single broad category of defect, suitable for genetic analysis, and the splitters who typically use statistical techniques such as factor analysis and cluster analysis to find large numbers of potentially separate syndromes (see e.g. Mattis et al., 1975; Doehring and Hoshko, 1977; Petrauskas and Rourke, 1979; Satz and Morris, 1981; Lyon et al., 1982; and Watson et al., 1983); see Kavale and Forness (1987) for an overview.

In its modern usage most researchers have probably been influenced by the crucial paper of Rutter and Yule (1975) (but even this is not entirely uncontroversial – see e.g. Rodgers, 1983, and van der Wissel and Zegers, 1985). Rutter and Yule argued against the then current definitions of dyslexia as being scientifically empty, and instead proposed an operational definition of specific reading retardation, which they contrasted with general reading backwardness. Nowadays dyslexia in the scientific literature is synonymous with specific reading retardation, and it will be so used here. Rutter and Yule defined general backwardness as attainment on a test of reading accuracy or comprehension two years four months or more below the child's chronological age, whereas specific reading retardation was defined as attainment on a test of reading accuracy or comprehension which was two years four months or more below the level expected on the basis of the child's age and IQ (using a multiple regression equation). (It should be noted in passing that Rutter and Yule emphasize the statistical fallacy of merely comparing reading age with intellectual age, due to the effect of regression to the mean). In a total population of 2300 9 to 11-year-old children they found 86 children (3.7%) who only met the criterion for specific reading retardation (SRR), 79 (3.4%) who only met the criterion for general reading backwardness (GRB), and 76 (3.3%) who met the criterion for both types of deficit. Statistically it is of course inevitable with a large population that some children will meet such a regression equation derived criterion. Demonstration that in fact they have separate syndromes requires external validation by demonstrating different biological, educational or social characteristics. Rutter and Yule showed that the groups differed in mean IQ (which is of course trivial since one group is defined in terms of its IQ being relatively high), but also that they showed significant dif-

ferences in sex ratio of boys to girls (SRR: 3.3:1, GRB: 1.3:1), in presence of definite organic brain disorder (SRR: 0%, GRB: 11.4%) in marked constructional difficulties (SRR: 7.0%; GRB: 19.0%), in moderate clumsiness (SRR: 12.8%; GRB: 24.1%) and motor impersistence (SRR: 14.0%, GRB: 34.2%). Similar results have been found by Jorm *et al.* (1986), who showed that GRB children show a range of other behavioural problems compared with controls, in areas such as attention deficit and behaviour problems, whereas those with specific reading retardation do not differ significantly from controls. Taken together these results clearly confirm the existence of a phenotypic category of SRR which can be distinguished by external criteria from GRB. It does not of course show that these differences are inherited (and indeed an intriguing aspect of Rutter and Yule's data is that there was no distinction between the groups in terms of the fairly vaguely defined family histories of reading difficulties (SRR: 33.7%, GRB: 35.6%) or speech delay (SRR: 10.1%, GRB: 8.6%)). A variant of Rutter and Yule's technique assesses the degree of specific reading ability as the residual score after variance from other tasks of intellectual ability or achievement has been partialled out, and compares that measure with similar specific measures of other intellectual abilities (such as mathematical, verbal or non-verbal processing); different patterns of correlation confirm the existence of specific intellectual abilities, which are themselves different from overall intellectual ability defined as the principal component of the different tests (McManus and Mascie-Taylor, 1983).

The study by Rutter and Yule (1975) shows the twin characteristics of a good study of classification: a classification derived from clear theoretical reasons, with validation of the groups against external predictive criteria.

Reviewing newer attempts to classify learning disorders in general, Morris (1988) has rightly criticized many of the classifications for not meeting simple empirical criteria of reliability and validity, for not being useful practically in communication between practitioners or researchers, and providing no indications of differential treatment. In searching for newer typologies Morris also emphasizes that classifications which are useful for one purpose (such as treatment) may not be useful for another purpose (such as understanding aetiology).

In the context of genetic models of dyslexia, it cannot be emphasized sufficiently that a single phenotypic condition may be the result of a number of discrete and separate genetic processes (for example in the case of human albinism, for which the two distinct types, tyrosinase positive and tyrosinase negative are indistinguishable phenotypically at birth, despite being due to different allelic mutations); as Decker and Bender (1988) have put it, 'phenotypic homogeneity does not mean genetic homogeneity'. Conversely, a single genetic defect may result in a range of different phenotypes according to the action of

external, environmental factors, or due to other genes (epistasis). Once more, as Decker and Bender have said, 'genetic homogeneity does not mean phenotypic homogeneity.' Finally it must be emphasized that there may be subsets of the dyslexic population which represent rare genetic causes of little relevance to the problem as a whole (as for instance in the newly described autosomal dominant syndrome reported by Stormorken *et al.*, 1985, of dyslexia, thrombocytopathia, asplenia, miosis and ichthyosis).

Classification of dyslexic subtypes should also be driven by theoretical distinctions derived from the cognitive analysis of normal reading, as revealed both in normals, and in those suffering from such deficits as the acquired dyslexias (see Ellis, 1984 for an introduction) and by tests derived from neuropsychological investigation. The strength of such an approach can be seen by comparing two recent studies. Lawson and Inglis (1985) have shown that factor analysis of the WISC-R intelligence test for children (Wechsler, 1974) produces two separate factors, of which the smaller, accounting for 9.9% of the variance, shows abnormal values in the reading disabled children reported by Rugel (1974). However consideration will reveal that since half the WISC tests are broadly verbal, as is reading, then this classification will of course correlate with that originally put forward by Yule and Rutter (1975); the lack of specificity of the measure is shown by it also being adequate at distinguishing learning disabled children in general from controls, and also in assessing the effects of unilateral brain damage. By contrast Smith *et al.* (1986a) examined a group of affected dyslexics and compared them with unaffected family members on a range of achievement and intelligence tests; they also used 14 neuropsychological tests, including naming, sentence repetition, auditory discrimination, motor and perceptual tasks. Cluster analysis of the entire group distinguished two separate clusters, of which one was particularly poor at reading and spelling. More interestingly cluster analysis of just the affected individuals revealed the presence of three distinct clusters. But it is was only the neuropsychological tests which showed different profiles between the three clusters; the achievement and intelligence tests showed the same profile in all three groups. The implication is that conventional measures of reading ability are unlikely to produce separate clusters of dyslexics; they merely distinguish affected from unaffected individuals. If there are separate types of dyslexic individuals then they will be revealed by measures that separate modular cognitive components in the process of reading. To take an analogy, ever more sophisticated measures of height will not help to tease apart the genetics of dwarfism – for that one needs biochemical measures which assess the efficacy of the normal pathways involved in growth hormone release and action. However a final twist in the analysis of phenotypes by cluster analysis is that although Smith *et al.* (1986)

appear to have found phenotypic clusters, they themselves do not believe that this clustering is important for genetic models. They showed that there is no association of clusters within families, which would have been expected had a specific mutation resulted in a specific phenotypic sub-type of dyslexia being passed down from parents to child. A similar conclusion was reached by Elbert and Seale (1988) who reported a detailed analysis of an extended kindred showing autosomal dominant inheritance with six affected members and 10 unaffected members, and found 'a high degree of phenotypic variability'. Ho *et al.* (1988) attempted to classify monozygotic (MZ) and dizygotic (DZ) twins according to the classification proposed by Bannatyne (1971); six out of nine MZ pairs (67%) were concordant for the Bannatyne sub-type, compared with three out of 10 DZ pairs (30%), a non-significant difference. Finally, DeFries and Decker (1982), using the sub-types of Decker and DeFries (1981), could find no significant evidence for clustering of sub-types within dyslexic families.

Taken overall the current literature on the classification of dyslexic syndromes suggests that there may well be different sub-types of dyslexia. They are distinguished principally by neuropsychological and cognitive tests, rather than by more refined measures of intelligence or achievements. But these sub-types are still not well enough defined empirically, with adequate reliability and validity; this results in confusion between studies. Finally there is at present no reason to believe that the sub-types are inherited differently since in the studies which have examined families of dyslexics there is no evidence that sub-types are associated within families.

Evidence for Genetic Effects in Dyslexia

Family Studies

Soon after the first clinical description of dyslexia, or 'congenital word blindness', was reported by Morgan (1896), there were reports in the literature of cases which seemed to run in families (e.g. Fisher, 1905; Hinshelwood, 1907, 1911; Stephenson, 1907; Thomas, 1905; Plate 1910), and further reports followed through the next half century (e.g. Illing, 1929; Orton, 1930; Laubenthal, 1936; Ronne, 1936; Marshall and Ferguson, 1939; Norrie, 1939; Skydsgaard, 1942; Kagen, 1943; Eustis, 1947a,b; Ramer, 1947; Hallgren, 1950; Walker and Cole, 1965; Mattlinger, 1967; McGlannon, 1968; Owen *et al.*, 1971). These early studies suffered from two major theoretical problems. Firstly they did not produce any comparison figures for the families of non-dyslexic children; and secondly the studies

only demonstrated familial associations, which do not necessarily imply genetic transmission, since families share not only genes but also culture and environment. The latter point occasionally annoys practising clinicians, as for instance Critchley (1970), who takes Rutter's (1968) re-iteration of the old genetic truth to task: 'These criticisms strike one as belonging to the category of special pleading, if not sheer shadow-boxing. To anyone experienced in clinical diagnosis, it seems impossible to overlook the very real heredo-familial incidence in cases of specific developmental dyslexia' (p 90). But clinical intuition has often been wrong in the past in matters of aetiology as opposed to diagnosis – witness nineteenth century claims from familial coincidence that tuberculosis was inherited, or in the twentieth century that AIDS was due to the toxic effects of amyl nitrate. A more formal approach is therefore essential.

Two separate studies in the 1970s confirmed the familial nature of dyslexia. Both Owen *et al.* (1971) and Foch *et al.* (1977) (see also DeFries *et al.*, 1978 and DeFries and Decker, 1982) compared reading-disabled children with matched controls, and they assessed the ability of the siblings and parents of both groups. Both studies showed higher rates of reading difficulties in the siblings and parents of dyslexic children than in the siblings and parents of controls. The data therefore provide convincing evidence that dyslexia does indeed run in families, but not that it is necessarily genetic.

Adoption Studies

Adoption provides a convincing test whether familial association is the result of transmission through shared genes or shared environment if the phenotype is shown to be more highly correlated with the phenotype of the biological parents than with that of the adoptive parents. DeFries and Plomin (1983) quote Cavalli-Sforza (1975) as saying that 'in the absence of adoption studies there is no hope of distinguishing rigorously whether standard measurements of inheritance . . . are due to genetic determination . . . or to socio-cultural inheritance'. I am unaware of any study in the literature which reports an adoption study of specific reading retardation, or of reading ability in general. That is surprising given the existence of large systematic adoption studies such as the Minnesota Adoption Studies (Scarr and Weinberg, 1983), the Texas Adoption Project (Horn, 1983) and the Colorado Adoption Project (Plomin and DeFries, 1983). DeFries and Plomin (1983) demonstrate that there are no intrinsic difficulties in carrying out a study using the adoptees' family method. Despite the lack of studies of specific reading ability it is of interest that the Minnesota Adolescent Adoption Study did find higher correlations in overall reading ability between biological siblings (0.27) than between adoptive siblings (0.11), but the study did not attempt to partial out overall intellectual

ability, and the effect was of similar size in all the four measures of aptitude and achievement (Scarr and Weinberg, 1983).

Twin Studies

The comparison of members of monozygotic (MZ) twin pairs – which are genetically identical – and dizygotic (DZ) twin pairs – which share only half of each other's genes – has always been a favourite method of assessing the genetic component of a characteristic. For biochemical and other physiological measures it is perfectly adequate, but for psychological measures it is more problematic, since in order to infer that increased similarity within MZ pairs is due to increased genetic similarity it is necessary also to make the assumption that environmental effects are the same for MZ and DZ pairs. That assumption is doubtful for many behavioural variables since it is immediately obvious to the eye that many parents treat MZ twins more similarly than they treat DZ twins (e.g. they dress them identically, etc.). The only strict way round this problem is either to study MZ twins who have been separated at birth, or to study the singleton offspring of MZ twins; in neither case, to my knowledge, have studies of reading disability been carried out.

The traditional way of analysing twin data for genetic effects is by showing a greater concordance in MZ than DZ twins. Table 6.1 summarizes existing data in the literature on twin concordance for reading disability (variously defined). It is worth noting in passing that the study of Bakwin (1973) actually refers to only 31 MZ and 31 DZ twin pairs in which at least one member is dyslexic, rather than the 57 + 40 pairs reported by McGuffin and Gottesman (1985) or the 676 twins (i.e. 336 pairs) implied by the equally influential Yule and Rutter (1985). The early studies show strong evidence for greater MZ similarity, although the most recent study of Stevenson *et al.* (1987) shows no evidence for a convincing heritable component in specific reading disability. Pennington and Smith (1988) speculate that the difference may be a function of the older age of Stevenson *et al.*'s sample, although no

convincing evidence is presented for that hypothesis, and it seems unlikely given that in general longitudinal studies of cognitive abilities in twins suggest a greater concordance in older MZ twins (Wilson, 1983).

More recent methods for examining twins have tried to use all of the information implicit in the continuous measures of reading provided by most reading tests, and have also tried to include twin pairs in which neither twin merits formal classification as a 'case' but nonetheless may have a low reading score relative to population norms. Matheny and Dolan (1974) showed that in 70 pairs of same-sex twins the intra-class correlation for reading scores was higher in MZ than in DZ twins, as had also been reported in several earlier studies (Newman *et al.*, 1937; Husen, 1953, 1960; Vandenberg, 1962); in none of these studies was an attempt made to partial the general intellectual component from that due to specific reading ability. Stevenson *et al.* (1987) analysed a population-based sample of 285 twin pairs, and partitioned the variance of test scores into genetic and environmental components: on the Schonell Reading test, after adjusting for IQ, 29% of variance was due to genetic components. Using a newer method, DeFries *et al.* (1987) considered data from twin pairs in which one member had already been identified as being reading disabled. They reasoned that regression to the population mean should be greater if members were genotypically (and hence phenotypically) discordant, than if they were concordant. That was indeed the case in their study of 64 MZ pairs and 55 DZ pairs in which the proband was dyslexic. Taken overall they estimated that 30% of the reading deficit in probands occurred due to heritable factors. It is not clear whether these twins (who form part of the 'Colorado Reading Project') are also the same as those reported by Ho and Decker (1988) as part of the 'Colorado Twin Study of Reading Disability' in which 30 MZ pairs and 30 DZ pairs were reported, one member of each also being reading disabled, and which showed a heritability by the same method of 86% for a composite reading score (see their p 104, $B_3 = 0.86$, table IV). Whether or not the data are the same, there is a clear discrepancy in the estimates of heritability.

Table 6.1 *Twin studies in dyslexia.*

MZ		DZ		
n	% concordant	*n*	% concordant	
11	100	27	33	Hermann (1959)
17	100	34	35	Zerbin-Rudin (1967)
31	84	31	29	Bakwin (1973)
14	100	?	40	Weinschenk (1965)
30	85	60	55	Decker and Vandenberg (1985)
17	35	32	31	Stevenson *et al.* (1987)

A final variation on the theme of twin studies in reading deficits, is that reported by Olson *et al.* (1989), who used MZ twins to assess the heritability of two separate types of reading process, derived on theoretical grounds from the dual process theory hypothesized from studies of adult patients with acquired dyslexia. Phonological coding in single word reading showed a significant heritability (0.46), whereas orthographic coding in single word reading showed no significant heritability. In fact all of the heritability in reading was accounted for by the phonological component. This result is compatible with the finding of Pennington *et al.* (1986) that adult dyslexics (with a family history of autosomal dominant-type dyslexia) typically show spelling errors which are phonological rather than orthographic in form; that is, they occur in the type of process that seems principally to be under genetic control.

Taken overall the studies of twins are surprisingly unimpressive, despite the claims of Pennington and Smith (1988) that they 'go beyond demonstrating genetic influence in dyslexia and help to specify what the heritable phenotype is' (p 280), and the optimistic conclusions of Harris (1986). The studies are heterogeneous, show generally low degrees of heritability, and make no serious attempt to differentiate different environment in MZ and DZ twins from different genetic contributions. A study of the reading skills of the offspring of MZ twins is urgently required to put the whole topic onto a more solid genetic foundation; it is hardly sufficient, as do Ho and Decker, merely to slip in a caveat such as 'assuming an additive model, random mating and equal environments for MZ and DZ twins pairs' (p 105), particularly since other data suggests that dominance variance may be substantial, mating is not random, and the assumption of equal environments is empirically testable. Nevertheless despite such criticisms, it does seem to be the case that twin studies overall probably indicate a genetic component to dyslexia – and that it would be special pleading to pretend otherwise.

Specific Genetic Models of Dyslexia

The studies described thus far have provided suggestive (although far from conclusive) evidence for a genetic contribution to reading ability and dyslexia. However they have not provided any specific genetic models which can account for the intra-familial correlations. Two broad types of genetic model must be differentiated: polygenic in which a large number of genes all have small, independent effects upon an ability, and tend to result in a normal distribution of the ability in the population (intelligence or height are good examples); and major genes in which several alleles at a single locus cause a small number of discrete behavioural categories in the population (typical examples being phenylketonuria or colour blindness). Major genes can come in different types (typically recessive, dominant or sex-linked), and polygenic models can also be modified to give threshold models, in which the polygenes are assumed to modulate an underlying latent variable which, if it exceeds some critical threshold, results in a discrete abnormality. Accounts of the models and their implications can be found in any good text book of genetics (e.g. Cavalli-Sforza and Bodmer, 1971) or behaviour genetics (e.g. Plomin *et al.*, 1989), or in specific reviews (e.g. Pauls, 1983).

Early investigators considered a number of genetic models. Hallgren (1950) carried out a segregation analysis of the patterns of inheritance within families and concluded on the basis of the high incidence of affected children (45.7%) from a cross between one affected and one unaffected parent that the condition was inherited as an autosomal dominant. (Similar figures have been reported by Vogler *et al.* (1985) for the risk in first-degree relatives, with similar values for transmission from affected fathers or mothers to sons (40% and 35% respectively) and to daughters (18%). Subsequent workers have however disputed the autosomal dominant interpretation. Sladen (1971) pointed out sex differences in Hallgren's data and suggested that the condition may have variable dominance in males and be recessive in females. Finucci *et al.* (1976) in their family study could find no consistent pattern of segregation to the pedigrees and concluded that the disorder was genetically heterogeneous. Foch *et al.* (1977) rejected a simple autosomal dominant model on the basis that the mothers of their reading disabled probands were not impaired, but also rejected a sex-linked inheritance on the basis that fathers were impaired. DeFries and Decker (1982) provided evidence for the presence of a major gene by showing that the variance in reading ability in the siblings and parents of learning disabled probands is greater than in the siblings and parents of controls, which is compatible with a major gene (and indeed a polygenic model would predict a decreased variance in these groups). DeFries and Decker (1982) rejected the possibility of sex-linked inheritance (proposed by Symmes and Rapoport, 1972) on two grounds: that the observed sex-ratio is incompatible with observed rates of dyslexia in the general population; and that the detailed parent-child correlations in ability were incompatible with that predicted by a sex-linked system (in which the father-daughter and mother-son correlations should be equal, and both should be greater than the mother-daughter correlation, which should in turn be greater than the father-son correlation). Finally in their search for a major gene, DeFries and Decker (1982) carried out a general segregation analysis and found clear evidence for bimodality, as had Lewitter

et al. (1980), which was consistent with a major gene, but then could find no single model which described all the data well. That was also the case for the data from the males alone, but for the females alone they could not reject a model of autosomal recessive inheritance. DeFries and Decker also assessed the adequacy of a polygenic threshold model. Since females are less likely to be affected with dyslexia than males it must be the case for a polygenic threshold model that the relative threshold for a defect is higher in females than males. Either the absolute threshold is the same for males and females but the means of the distributions are different in the two sexes (e.g. Pennington and Smith, 1983), or the means of the distributions are the same but the absolute thresholds are different. Affected females will therefore be further from the population mean than will affected males; hence they should share with their relatives the genes that produced a greater deviation from the population mean, so their relatives should also show a higher incidence of reading disability. That was precisely what was found, 75.8% of the fathers of female dyslexics were reading disabled, compared with 36.5% of male dyslexics, and 58.6% of mothers of female dyslexics were disabled compared with 29.2% of mothers of male dyslexics. Vogler and DeFries (1985 and 1986) have explicitly tested polygenic models in the families of learning disabled probands and in normal controls, using either bivariate or multivariate path models which explicitly make the assumption that multivariate normality underlies the measured variables. In both cases they find that variation in reading ability within the families of control children can be well-explained by means of a polygenic model, but that the model does not fit the families of the reading disabled children. The implication is clearly that polygenic variation is important in the normal range; but that it alone cannot account for reading disability.

A major problem with dyslexia, as with any complex condition, is that it may be multifactorial in origin, being caused by a number of different genetic processes. A clear example of this process is seen in mental subnormality. Roberts (1952) postulated that less severely mentally retarded cases may represent the lower end of a normally distributed continuum in the population (people who could be considered as having had a poor deal in the polygenic genetic lottery), whereas more severely retarded children are the result of specific effects of individual major genes which cause specific biochemical defects. This view is now the accepted orthodoxy for mental retardation (Zigler and Hodapp, 1986), which thus differentiates 'organic' from 'familial' retardation. These two categories can broadly be distinguished by severity, the former *group* tending to be severely impaired while the latter are mildly impaired. Finucci and Childs (1983) used a similar approach in dyslexia *to* distinguish severely

impaired readers from mildly impaired. Severely disabled children had relatively unimpaired parents (perhaps implying a recessive mode of inheritance), whereas the mildly impaired children had severely impaired parents (perhaps reflecting parental polygenic mixing, coupled with regression to the mean). In addition severely impaired children had siblings who tended to assort in two types, normal and severely impaired (again suggestive of a major locus), whereas mildly impaired children tended to have mildly impaired siblings (compatible with a polygenic form of inheritance). Finally, Finucci and Childs reported evidence that dysphonetic spelling errors were common in the severely disabled children and rare in the mildly impaired children, suggesting two distinct types of syndrome, and that the type of spelling error was significantly associated between parents and children. Taken overall, these data suggest that mild and severe dyslexia may well have different genetic bases, and that a single model of the inheritance of reading disability is unlikely.

Summarizing the results of specific genetic model fitting, it seems no single model, polygenic, threshold or major gene, is going to account for the entire range of reading ability from normal through to dyslexic. There seems little doubt that reading ability in the normal range is partially under polygenic genetic control (although studies often have not fully partialled out overall intellectual ability, which is also under polygenic genetic control). A proportion of mildly reading disabled children will therefore be the result of poor polygenes, akin to the 'familial' causes of mental retardation. For the severely disabled group the most successful model suggests a polygenic threshold, particularly since it accounts for the large sex differences; and that polygenic variation is probably, but not necessarily, the same variation as for individual differences in reading ability in the normal range. Finally it may be the case that there is a heterogeneous selection of autosomal (but not sex-linked) major genes, particularly since it is necessary to account for the increased variance of ability in the families of reading disabled children.

Assortative Mating

A complication of any genetic study is that the implicit models derived from animal husbandry and laboratory studies of *Drosophila* or mice tend to assume that mating is random within the population. That assumption is rarely true for human populations (as for instance is shown by the high degree of assortative mating for such variables as intelligence, social class or height (e.g. McManus and Mascie-Taylor, 1984)). Assortative mating for reading ability is substantial (typical correlations between parents being of the order of 0.3). Of particular interest is that this correlation seems to be similar both in the parents of control children and reading disabled children (DeFries and

Decker, 1982; Vogler and DeFries, 1985, 1986); the implication is that poor readers are not only more likely to pass genes for poor reading to their children but that they are also more likely to find a spouse who will also pass on genes for poor reading ability. As a social phenomenon it is worth noting that assortative mating for reading seems to be higher than for other measures of intellectual processing, showing both the high premium placed upon reading ability in society, and the ease with which it is perceived by other individuals.

Genetic Linkage Studies

For a number of years Smith and Pennington have been investigating the possibility that a major gene for dyslexia may be located on human chromosome 15 (see e.g. Smith, 1978; Smith et al., 1980, 1983a, 1986; Pennington and Smith, 1988; Lubs et al., 1988). Demonstration of linkage with a known genetic marker (see Kimberling, 1983; Smith and Goldgar, 1986) has two important implications: firstly it can provide indubitable evidence of a genetic contribution to a process, and secondly it can tell one the approximate location of the gene in the genome, thereby allowing eventual isolation and characterization of the gene through the process of 'chromosome walking'.

Smith and Pennington have studied a slowly growing series of families which were characterized by having evidence of reading disability in three generations in relatively extended pedigrees (see Smith et al., 1983b for examples of pedigrees), and which was apparently inherited in an autosomal dominant fashion; by 1988 they had analysed 245 individuals in 19 extended families. It should be noted that the assumption of autosomal dominance does not preclude the possibility of other forms of inheritance, or bias the linkages that might be found, since the method for detecting linkage was unlikely to be sensitive to anything other than this particular form of inheritance. Genetic markers were examined by looking at blood groups, isoenzymes, chromosome heteromorphisms, and other genotyping markers (e.g. tongue rolling and PTC tasting).

Of 23 markers tested, one produced significant linkage with dyslexia; this was a heteromorphism for fluorescent staining of the chromatin of chromosome 15 (see Smith et al., 1983b for an example). This linkage was significant using the conventional criterion of a lod score (likelihood odds ratio) of greater than 3, which is conventionally stated as equivalent to $P < 0.001$. However it should be noted that this level of significance is not quite as dramatic as it might seem. A lod score of 3 is conventionally chosen as a criterion because it approximately represents a conventional posterior significance level of $P < 0.05$ adjusted to take account for the prior odds of a gene having to be on one of the 23 chromosomes as being approximately 1 in 20

(although see Smith et al., 1983b for a possible justification for using the 1 in 1000 figure without correction for prior odds). In effect, therefore, multiple significance testing occurs because there are 23 chromosomes, with linkage potentially occurring on any of the independent crossovers that occur (Morton, 1955). The confusion of the true meaning of a lod score of 3 is shown in two papers in the same issue of *Nature*; in one a lod of 3 was treated as $P < 0.05$ and in the other it was treated as $P < 0.001$ (Kelsoe et al., 1989; Robertson, 1989). Furthermore this is the nominal alpha significance level for a *single* test of linkage. If tests are repeated then some form of adjusted significance testing should be used (as in the conventional Bonferroni procedure).

In addition the multiple markers used by Smith and Pennington mean that one should be wary of their result. This is particularly the case as examination of their original linkage results shows that most of the significant linkage was due to a single family (number 432) which contained 15 members, and that few of the other seven families contributed anything to the lod score, and that one family (number 491) almost showed a significant negative lod score for the absence of linkage. More recent work (Smith et al., 1986; Pennington and Smith, 1988) has confirmed that there is indeed significant genetic heterogeneity in the families, with the suggestion that only about 30% of 16 families carry the gene on chromosome 15. Pennington et al. (1987) have compared the pattern of reading and spelling errors shown by individuals in pedigrees which are apparently linked to chromosome 15 with those which are not, and have found no differences: both groups were principally deficient in phonological coding. This result is compatible with the finding of Olsen et al., mentioned above, that it is principally phonological rather than orthographic processes which are under genetic control. A similar result was reported by Pennington et al. (1986). These negative results, however explained, cannot provide support for the idea that chromosome 15 linkage families are a separate subset of dyslexics. The ultimate test for any claim to linkage, which transcends all statistical considerations, is that other workers can replicate the result. As yet only one published study has attempted a replication (Bisgaard et al., 1987), and that failed to find evidence of any linkage with chromosome 15 heteromorphisms. However since it contained only five families it is conceivable that this was insufficient to find a gene present in only 30% of families.

One recent piece of evidence may possibly corroborate the presence of a gene controlling reading ability on chromosome 15. The Prader-Willi syndrome consists of obesity, mental retardation, short stature and infantile hypotonia, and has been associated with an interstitial deletion of chromosome 15q11-q13 in about 60% of patients (Ledbetter et al., 1987), the deletion coming from

the paternal chromosomes. Intriguingly individuals with an apparently identical 15q11–q13 deletion, but of maternal origin, have a different syndrome, the Angelman or 'happy puppet' syndrome, of large mandible, protruding tongue, jerky, coarse motor movements and paroxysmal laughter, ataxia and epilepsy (Donlon, 1988). Children with the Prader-Willi syndrome, but without a deletion, have now been shown to have two chromosome 15 regions derived from the mother, and none from the father; like the deletion cases therefore they lack a paternal contribution to chromosome 15 (Nicholls *et al.*, 1989). Burd and Kerbeshian (1989) have reported the case of a patient with the Prader-Willi syndrome who did not have the 15q11–q13 deletion (and therefore presumably had two material contributions) but who did have an associated hyperlexia (i.e. disproportionately good reading skills given the overall level of intellectual achievement). It is too early as yet to assess the importance of these findings for an understanding of dyslexia, and the result may merely be a coincidence. First therefore the result must be replicated. However the differential effects of chromosomes from maternal and paternal sources (so-called genetic imprinting) could be of importance in explaining the overall sex-ratio in children with language disorders, and also the otherwise mysterious (also unreplicated) finding of an increased sex-ratio in the siblings of affected offspring of language-disabled mothers (but not fathers) (Tallal *et al.*, 1989). Tallal *et al.* do point out that for the specific case of dyslexia impairment rates are equal for the sexes in the siblings of affected children, but this still allows the possibility of an overall deviation in the sex-ratio in these siblings. Since the sex-ratio in the population is normally extremely well conserved, any deviation from it always requires a biological explanation.

Taken overall, the only evidence at present for genetic linkages to dyslexia is on chromosome 15, but the findings are not compelling, and until there is unequivocal replication it is probably premature to conclude that a major gene for dyslexia exists in this region. Even if the linkage is confirmed it probably will not account for more than one in three of cases in families which show an autosomal dominant mode of inheritance. Further work is urgently required on this topic. If the linkage can be confirmed then it will be very important in dissecting the genetic contributions to dyslexia, and in understanding the nature of the phenotype.

Chromosomal Abnormalities and Dyslexia

Abnormalities of chromosome number are often associated with abnormalities of cognition (as in the mental retardation associated with Down's syndrome, trisomy 21). A few investigators have studied the verbal skills, and

particularly the reading ability, of individuals with sex chromosome abnormalities. Individuals with karyotypes of 47,XXY (Klinefelter's syndrome), 47,XXX, 47,XYY and 45,XO (Turner's syndrome) have been studied. They all show a tendency towards mildly reduced IQ; but it has also been found that those with an additional sex chromosome (XYY, XXY, XXX) tend to have decreased verbal ability, whereas those with a deficit of sex chromosomes (XO) seem to have a decreased spatial ability (Netley, 1983; Pennington and Smith, 1983). This result is of undoubted interest to the general question of the development of linguistic ability. Also it has been interpreted by Crow (1989) as evidence for a gene for cerebral dominance in the pseudo-autosomal region of the X chromosome. But these cases throw little light on the specific question of genes for reading ability. The only study which has reported specific problems with reading ability in subjects with chromosomal abnormality is that of Bender *et al.* (1986a) (see also Decker and Bender, 1988; Bender *et al.*, 1986b), in which boys with a 47,XXY karyotype seemed to have a specific deficit in reading ability, despite relatively good overall intellectual and verbal abilities. No very obvious explanation for these results is apparent, and in the absence of adequate comparative data on other sex chromosomal anomalies, conclusions are difficult. Another intriguing result which may not be relevant to reading *per se*, although it is almost certainly of importance for language development in general, is that of Netley (1983); in XXY and XXX children, a low total dermal ridge count (TDRC), which reflects a slower than normal growth rate in early and mid fetal life, is associated with a greater deficiency in verbal intelligence (Netley and Rovert, 1982), and with dichhaptic and tachistoscopic asymmetries consistent with atypical, right hemisphere processing (Netley, 1983). Although it is unclear as yet what the mechanism might be, it is possible that similar processes may interfere with the development of reading skills.

It would be of great interest if chromosomal deletions or other abnormalities of the autosomes had been reported in association with dyslexia, since these might point to a possible locus for a gene controlling dyslexia. However to my knowledge no such associations have ever been reported. However there do not seem to have been any systematic studies of the karyotypes of dyslexic individuals.

Spelling Defects as Distinct from Reading Deficits

Reading and spelling are separate but related processes. Although each requires a knowledge of the relationship between the individual graphemes of which words are made and their relationship to the phonemes which constitute the basic linguistic elements of spoken language,

there is a fundamental difference between them: reading requires a translation from graphemes to phonemes, whereas spelling requires a translation from phonemes to graphemes. Since the processes are in principle distinguishable, if they are separate then patients should be found who are capable of one process but not the other: so-called 'double dissociation'. The cognitive neuropsychology of spelling, and its relation to reading and writing, is complex (see Margolin, 1984; Ellis and Young, 1988; Shallice, 1988), but taken overall it seems there are certain separable modular systems carrying out distinguishable cognitive operations in reading, writing and spelling. If that is the case then these component processes may be under separate cognitive control. Frith (1980) has demonstrated that poor spellers who are good readers make different spelling errors from poor spellers who are bad readers, and Bryant and Bradley (1980) have shown that children can often spell words that they cannot read; in each case the implication of these dissociations is that the two processes are separable. As mentioned earlier, Finucci and Childs (1983) have found evidence not only that severely dyslexic children are more likely to make dysphonetic spelling errors than are mildly reading retarded children (which may merely represent a simple severity gradient), but also that there is a within-family association between the degree of dysphonetic spelling errors. These results suggest that reading disability and spelling difficulty may be to some extent under separate genetic control. That possibility is supported by the twin study of Stevenson *et al.* (1987). They found little evidence that specific reading disability had a higher concordance in MZ than DZ twins; but they did find a higher, although still non-significant, concordance rate for spelling difficulty in MZ (50%) than DZ (33%) twins. When variation in ability across the entire range was considered the scores on the Schonell Spelling test showed a far higher heritability (73%) than did scores on the Schonell Reading test (29%), with almost all of the environmental variation in spelling being due to specific environment (16%) rather than common environment (2%), suggesting that within family factors were of relatively little importance in spelling. Pennington *et al.* (1986) have shown in 12 families in which there was autosomal dominant dyslexia that spelling was normal for orthographic features, but was impaired only on phonological features. To what extent this is typical only of this subset of dyslexics is not clear, since no studies have reported individuals with orthographic problems, and Pennington *et al.* imply that there is no difference between those families with a chromosome 15 linkage and those without.

In summary, there is some suggestive evidence that spelling may be under separate genetic control from reading, although at present the data are far from compelling. Future studies should routinely collect measures of both reading and spelling in order to separate the processes, and should classify errors as orthographic or phonological.

The Evolution of Specific Genes for Reading, Writing and Dyslexia

If there is a genetic component to dyslexia then the implication must also be that there is a genetic contribution to normal reading ability (although that is not in fact strictly necessary). If there is a genetic basis to reading ability then this raises particular problems, since all of the evidence suggests that reading and writing only developed in human societies around 3500 BC i.e. about 5500 years ago. That is a short time in evolutionary terms, and therefore it has been argued that it is too short for a specific gene for reading or writing to have evolved, and fixed (e.g. Annett, 1985; Corballis, 1989). In fact Shallice (1988; pp 68, 77) and Ellis and Young (1988; p 187) have gone further and argued that this short time is completely incompatible with a genetic process; hence they suggest that the modules for reading and writing must have resulted from the culturally-mediated environmental effects of writing itself. But simple classic genetic modelling demonstrates that, in the 300 or so generations which have passed since writing evolved, a gene with even a fairly small selection coefficient could simultaneously have evolved and fixed (McManus, in preparation). If one allows the quite reasonable possibility of co-evolution of genes and culture (Cavalli-Sforza and Feldman, 1981; Boyd and Richerson, 1985; Feldman and Cavalli-Sforza, 1989), then selection rates could have been even further speeded up. If reading and writing can be the result of a gene (or genes) then the possibility arises either that the genetic basis for dyslexia represents the 'wild-type' alleles that have still not been completely eliminated from the gene-pool, or that they represent further mutants of the reading/writing genes themselves.

Indirect Genetic Theories of Dyslexia

The genetic theories of dyslexia discussed thus far have all been direct in the sense that the genes in question have been postulated to be the immediate cause of variation in reading or writing ability. However within the past decade several theories have also developed which might be called indirect genetic theories, in the sense that they predict that dyslexia should run in families, but that control of reading ability is not the principal purpose of the gene; hence dyslexia emerges as a mere side-effect from the genetic process. All three of these theories are principally theories of cerebral lateralization, and to a great extent all fail if dyslexia cannot be shown to be associated with abnormalities or deviations from normal laterality.

1. McManus' Genetic Model

This is the simplest and the least developed of the indirect models. McManus (1979, 1984, 1985) proposed that handedness was determined by a simple genetic model in which there are two alleles, dextral (D) and chance (C), at a single genetic locus, with left-handedness occurring with probability 0 in the DD genotype, 0.25 in the DC genotype and 0.5 in the CC genotype. This model accounts well for the existing data on handedness in families and twins. By postulating pleiotropy for the gene so that it controls language dominance by a similar mechanism one can explain the association of handedness and cerebral dominance. By allowing the gene also to control a second language dominance process one can account for data on recovery from aphasia. By additionally allowing the gene to determine dominance for visuo–spatial functions the model explains the association between visuo–spatial and language dominance. Under this final model it becomes possible (and indeed likely) that a proportion of individuals will have language dominance, hand control and visuo–spatial functions in atypical hemispheres from the normal situation, such that sometimes several functions will be separated in different hemispheres when they are typically in the same hemisphere, and in other cases functions which should normally be in different hemispheres will be in the same hemisphere. Any of these deviations from normality could result in problems of integration between tasks, and might therefore result in difficulties with, say, integrating phonic language processes with the visuo–spatial processes involved in reading. The genetic model clearly predicts that individuals with such patterns of cerebral organization should have an increased rate of left-handedness and an increased rate of familial left-handedness. At present the model has not been formally tested beyond those predictions.

2. Annett's Right-Shift Model

Annett (1985) has proposed a genetic model of right-handedness and cerebral lateralization in which two alleles, $+$ and $-$, at a single locus determine the extent of 'right-shift', with $-/-$ genotypes showing no right-shift, $+/+$ genotypes showing a large right shift, and $+/-$ heterozygotes showing an intermediate shift. Individuals with a large right shift tend to be right-handed and left-hemisphere language dominant, whereas left-handedness and right-hemisphere language dominance are associated with an absent right shift. Annett (Annett and Kilshaw, 1984; Annett, 1985; Annett and Manning, 1990) has extrapolated from the theory to explain the presence of abnormalities of lateralization in dyslexia; only a brief account will be given here since the present volume contains a more extensive account by Annett herself (Chapter 6). In the 'Mark I' version of the model it was proposed simply that since dyslexics are deficient in some form of

linguistic ability, and linguistic ability is associated in evolutionary terms with left-hemisphere language dominance, then dyslexics should show an increased frequency of the $-$ gene (i.e. $-/-$ and $+/-$ genotypes). That hypothesis failed however when it was found that the mean right shift, as manifested in the difference in performance of right and left hands did not differ significantly between dyslexics and controls (Annett and Kilshaw, 1984, Table 6). However closer examination of the data revealed a greater variance in the asymmetry score in dyslexics and Annett therefore proposed, in the Mark II model, that dyslexics in fact had an excess both of $-/-$ and $+/+$ genotypes, and that the optimal genotype was the heterozygote, $+/-$. This hypothesis was then expanded by an interesting genetic hypothesis in which it was argued that since 49% of the population are heterozygotes, and that therefore the frequency of the two homozygotes is about equal, then the $+$ and $-$ genes must be maintained in a balanced polymorphism due to the equal disadvantages of the $-/-$ and the $+/+$ genotype. However the argument fails on genetic grounds since one can in fact infer nothing about the nature of a balanced polymorphism from the genotype frequencies (which will almost certainly satisfy the Hardy-Weinberg equilibrium). The heterozygote must indeed be at the greatest selective advantage (for otherwise there could be no balanced polymorphism – Cavalli-Sforza and Bodmer, 1971); but heterozygotes could actually be less common than one of the homozygotes and the polymorphism still remain balanced, the balance point depending simply upon the relative selective disadvantages of the two homozygotes.

Ultimately the Mark II Annett model, which is self-confessedly *post hoc*, rests entirely on the empirical observation that the variance in asymmetry scores is greater in dyslexics than controls. That observation itself must be controversial since dyslexics tend overall to be slower with both hands in comparison with controls (Annett and Kilshaw, 1984, Table 5). Hence the increase in variance in the L-R difference in dyslexics which is crucial to the hypothesis depends critically upon the joint distribution of performance in right and left hands being bivariate normal; any non-normality or non-linearity could readily produce an artefactual increase in the variance in one group or the other.

3. Geschwind's Theory of Cerebral Lateralization

In 1982 Geschwind and Behan proposed a theory of cerebral lateralization which, in part because of its novelty, theoretical breadth and its ability to integrate seemingly unrelated phenomena, has been very influential. The theory is complex; at least 30 independent causal processes are postulated (McManus and Bryden, in preparation). In consequence it is neither easy to describe nor to test. The

theory as a whole cannot be described here, although the central elements of relevance can be picked out. Of particular interest is that the theory originated from a consideration of the causes of dyslexia. Geschwind, at a November 1980 meeting of the Orton Society, after noting the association between dyslexia and left-handedness, suggested that researchers should look for associations between dyslexia and other diseases in dyslexics and in their relatives (Geschwind, 1986). In subsequent papers Geschwind and Behan (1982, 1984) described an association between left-handedness and a range of conditions, of which the most counter-intuitive were the immune disorders. That association stimulated a massive theoretical endeavour which was eventually published in three long papers and a book (Geschwind and Galaburda, 1985a,b,c, 1987). The theory revolves around the male hormone testosterone, of which high quantities during fetal life are proposed to have a range of effects: slowing of development of the left hemisphere, resulting in a right-hemispheric compensatory hypertrophy and left-handedness; abnormalities of neural migration, and hence cytoarchitectonic defects in the brains of dyslexics; and an impairment of the immune system, and hence the subsequent development of immune disorders. Left-handedness, dyslexia and immune disorders should therefore be inter-related, and since high testosterone levels are also associated with maleness each should also be associated with being male. Thus far the theory is not a genetic theory except in so far as maleness itself is genetically determined. The theory is however genetic because Geschwind and Galaburda propose a number of mechanisms whereby testosterone levels are themselves under genetic control (see McManus and Bryden, in preparation). The result is that in so far as high fetal testosterone levels run in families, so dyslexia, *inter alia*, should also run in families.

The Geschwind theory is complex and hence very difficult to test. There are no direct measures of fetal testosterone levels, and there is no evidence in man that testosterone causes the cortical cytoarchitectonic abnormalities reportedly associated with dyslexia. Nevertheless there is some evidence of cytoarchitectonic abnormalities in immune defective mice that are very similar to those in human dyslexics, and which might provide a good experimental model (Sherman *et al.*, 1989). A central empirical prediction of the Geschwind theory in relation to dyslexia is that dyslexics and their families should show an increased incidence of immune disorders. Pennington *et al.* (1987) have looked for such an excess and failed to find any evidence for it, although Urion (1988) has found some suggestive evidence, although there are reservations in the account of the study. Finally in Geschwind and Galaburda (1987), Kinsbourne and Bemporad are quoted in a personal communication as having found 'a higher

rate of immune disease in the families of dyslexics who were left-handed or had left-handed relatives than in the families of dyslexics without such histories'; as yet that study has still not been prepared for publication (Kinsbourne, personal communication, May 1989).

Taken overall the Geschwind theory can be seen as stimulating and interesting but, as yet, it is without the compelling evidence that would force one to accept its central basic premise that fetal testosterone is responsible for the vast panoply of processes in which it is implicated by Geschwind. As a genetic theory therefore its foundations are necessarily weaker still.

Indirect Theories: Overview

Taken together the three indirect genetic theories suffer from similar problems. Although couched in terms that are ostensibly genetic, in so far as they predict familial associations because of shared genes, in practice none has attempted to provide convincing data in their support that is specifically genetic. Ultimately any genetic theory qua genetic must study data in which meiotic divisions and recombination have occurred. One can never prove a genetic theory from mere observation of affected individuals, for that allows no method of partitioning variance. The three indirect theories, although interesting, do not meet this criterion and therefore it is ultimately an act of faith to argue that they need invoke genetic processes.

Evidence for Environmental Effects in Reading Ability

The genetic models of reading ability in the population find heritabilities which are low (of the order of 30% of variation accounted for by additive genetic factors) and therefore it is probably the case that a substantial amount of variance must be explained by non-genetic factors. Few studies have examined this question using sophisticated statistical methods in large samples.

Birth Order

Genes cannot know in which order they are going to be born. If therefore a characteristic shows a significant correlation with birth order (first-born, second-born, etc.) then non-genetic factors must be at work (and a similar argument applies to family size, since one particular set of genes cannot know how many children will subsequently be born into the family). The possibility was first investigated by Warburg (1911), who felt that dyslexia was particularly likely in the last-born child of a family. Anderson and Kelley (1931) found that first-born children were less likely to be affected by dyslexia, as did Bennett (1938).

However Hallgren (1950) could find no significant effect of ordinal family position, as neither could Naidoo (1972). Harris (1961) is described by Critchley (1970) as having reported that youngest or last-born children were twice as likely to be affected by dyslexia as are first-born children. However Critchley cites no reference for the paper, and the same Harris and Rosewell (1953) argued that dyslexia particularly often occurred both in first children and in last children. The data of Critchley (1970) himself certainly show that first-born children represent 30.1% of a series of dyslexic children as compared with an expected 62.6% given his population figures. Likewise Kawi and Pasamanick (1959) found that 34% of cases were first-born, compared with 50% of controls. Using a slightly different approach, calculating an index of specific reading ability in a national population sample ($n = 13\,808$), McManus and Mascie-Taylor (1983) found that specific reading ability was greatest in first-borns and declined linearly to fourth-born and above. In contrast there were no birth-order effects for the specific components of mathematics, verbal ability and non-verbal ability (although, as in many other studies (see Zajonc *et al.* (1979)) there was a strong birth-order effect upon general intellectual ability). It may be that a similar mechanism exists to that proposed by Zajonc (1983) in his confluence model for explaining the birth-order effect in overall intelligence, scarce within-family teaching resources being spread ever more thinly as family size and birth order increase. The model predicts independent effects of both birth order and family size, although few studies are large enough to have the statistical power to distinguish these components. It is also of some theoretical significance that there is no interaction between birth order and social class (McManus and Mascie-Taylor, 1983), thereby excluding any extension of the Zajonc hypothesis which argues that birth order is only of particular importance in low social class families in which intellectual resources may be in short supply. A final possibility is that cases of dyslexia can be divided into two types, familial cases and sporadic phenocopies, which are isolated cases within families without any evidence of a family history: birth order would only be important in the second group. To my knowledge no study has investigated whether parity effects are present only in cases without a family history; this should be investigated urgently, since if true then studies searching for genetic factors could then concentrate their attention on early-born cases.

Parental Age

In the same way that genes cannot know in what order they are going to be born, so it is unlikely that they can know the age of the parents (although there may be exceptions, as both maternal and paternal gametes show greater incidences of mutation and chromosomal abnormality with increasing age). However the finding of McManus and Mascie-Taylor (1983) that specific reading ability increases in relation to parental age (after taking into account social class and birth order) is unlikely to be explained by increased mutational rates, and seems to be a *prima facie* case of social influence upon reading ability. The study by Naidoo (1972) however found no differences in parental age between dyslexics and controls.

Other Correlates of Reading Ability

McManus and Mascie-Taylor (1983) showed also that specific reading ability correlated significantly with a number of other factors such as high social class, the presence of acquired myopia, increased height, residence in East-West Riding of Yorkshire or Wales, and giving up smoking prior to pregnancy, but that there were no significant correlations with parental age difference, obstetric complications, birth weight, maternal smoking during pregnancy or maternal blood group. Although of interest in their own right, these correlations, unlike those with birth order or parental age, cannot help in deciding whether reading ability is under genetic or environmental control. Hardly any of these significant correlations have been examined in dyslexic subjects in comparison with controls.

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