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Evaluating the Empirical Support for the Geschwind–Behan–Galaburda Model of Cerebral Lateralization

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The Geschwind–Behan–Galaburda (GBG) model of cerebral lateralization provides a complex but testable theory of the origins and associates of cerebral lateralization. An overall evaluation of the model suggests that it is not well supported by empirical evidence and that in the case of several key theoretical areas, the evidence that does exist is inconsistent with the theory. In particular: the concept of "anomalous dominance" is shown to be theoretically and methodologically flawed; a meta-analysis of the relationship between handedness and immune disorders finds a marginal overall association, and while three conditions (allergies, asthma, and ulcerative colitis) do show significant associations with left-handedness, two other conditions (myasthenia gravis and arthritis) show significant *negative* associations with left-handedness. Finally, a review of the ori-

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gins of the neural crest, and its associations, suggests there is almost no empirical support for the GBG theoretical model in this area.

In 1982 Geschwind and Behan published a short paper which had an almost immediate impact upon the neuropsychological community. The impression it made was principally due to its radical proposal that cerebral lateralization is intimately linked with levels of fetal testosterone, and with the functioning of the fetal and adult immune systems, and hence could explain a surprising range of putative associations between left-handedness and various diseases. The 1982 paper was followed in 1985 by three lengthy and complex papers in the Archives of Neurology (Geschwind & Galaburda, 1985a, 1985b, 1985c), which were also issued almost unchanged in book form two years later (Geschwind & Galaburda, 1987). These papers now articulated a complex, wide-ranging theory that encompassed a huge range of neuropsychological and biological phenomena, invoked a massive range of empirical support from a dozen or more subdisciplines, and seemed to have something important to say about almost every aspect of neuropsychology. The GBG model has become sufficiently popular in the eyes of the public that many of its tenets are taken for granted. Thus, Coren (1992), in his popular book on left-handedness, assures his readers that left-handers are more likely to suffer from immune disorders. Likewise, the potential association between left-handedness and AIDS derived from the model may be sufficiently well-known that it can be used to explain why left-handed homosexuals are more likely to be tested for HIV than are right-handed ones (Marchant-Haycox, McManus, & Wilson, 1991). The influence of the theory, which we shall henceforth refer to as the Geschwind–Behan–Galaburda theory (GBG) can be further gauged by examining citation counts for the various papers over the period 1986–1993 (Table 1); given that Smelser (1987) regards citation counts of as few as 100 as possible "citation classics," it is obvious that here we are dealing with a major scientific phenomenon, of sudden onset and immediate influence.

Despite such high frequency of citation (and implicit acceptance) by the scientific community, the theory is neither as straightforward as it seems, nor is its empirical support as strong as is often claimed. Indeed, elsewhere (McManus & Bryden, 1991) we have devoted considerable effort in attempting to disentangle all the diverse threads of the theory. At times we found this to be more akin to an exercise in hermeneutics than in conventional scientific exegesis. Ultimately, though, the GBG theory is indeed a *scientific* theory and, hence, must survive or otherwise on the basis of its empirical support; for theories that live by empirical evidence are also at risk of dying by them.

In this paper we ask what major areas of the GBG theory can be tested empirically, we review the quality of the evidence, and we evaluate the

TABLE 1
Citations of the GBG Model during the Period January, 1986, to March, 1993

	1986	1987	1988	1989	1990	1991	1992	1993
Geschwind and Behan (1982)	33	31	25	33	38	35	28	(28)
Geschwind and Galaburda (1985a)	17	42	29	35	40	38	45	(24)
(1985b)	13	24	14	12	22	14	24	(8)
(1985c)	12	16	12	15	17	11	14	(12)
Geschwind and Galaburda (1987)	—	2	9	15	23	17	24	(8)
Articles citing any of above	48	67	56	77	89	78	87	(56)

Notes. Figures for 1993 are for the period January to March only, and the figures in parentheses are therefore four times those actually found, in order to provide estimates for the whole of 1993. All citation counts are based on the CD-ROM version of the Science Citation Index. It is probable that more citations are present in the Social Science Citation Index or other data bases.

extent to which the theory is supported by that evidence. In so doing we accept that our overview of the massive set of possibly relevant data cannot be anything other than selective (for example, we do not review the animal literature), we realize that our emphasis upon particular areas may be seen as partial, and we acknowledge in advance that our conclusions can hardly be uncontroversial.

THE GBG MODEL: A SIMPLIFIED ACCOUNT

In an earlier paper (McManus & Bryden, 1991), we provided a detailed analysis of the Geschwind and Galaburda (1987) model of cerebral lateralization. The specific model has many complex ramifications, but a general overview of it is provided in Fig. 1. To simplify, alterations in the level of fetal testosterone are seen as having many effects. First, elevated testosterone levels lead to an alteration in the growth of the left cerebral hemisphere. This, in turn, has numerous consequences. It leads to effects on the development of language, resulting in developmental dyslexia, impaired language development, stuttering, and autism. At the same time, it also leads to changes in left hemipshere function that produce what Geschwind and Galaburda (1987) have termed anomalous dominance (AD), reflecting some combination of atypical handedness, language lateralization, and visuospatial lateralization. Furthermore, changes in the left hemisphere entail the development of an altered right hemisphere, resulting in modification of various cognitive abilities, especially those involving spatial ability, music, and mathematics. In addition, elevated testosterone affects the thymus, resulting in disorders of the immune

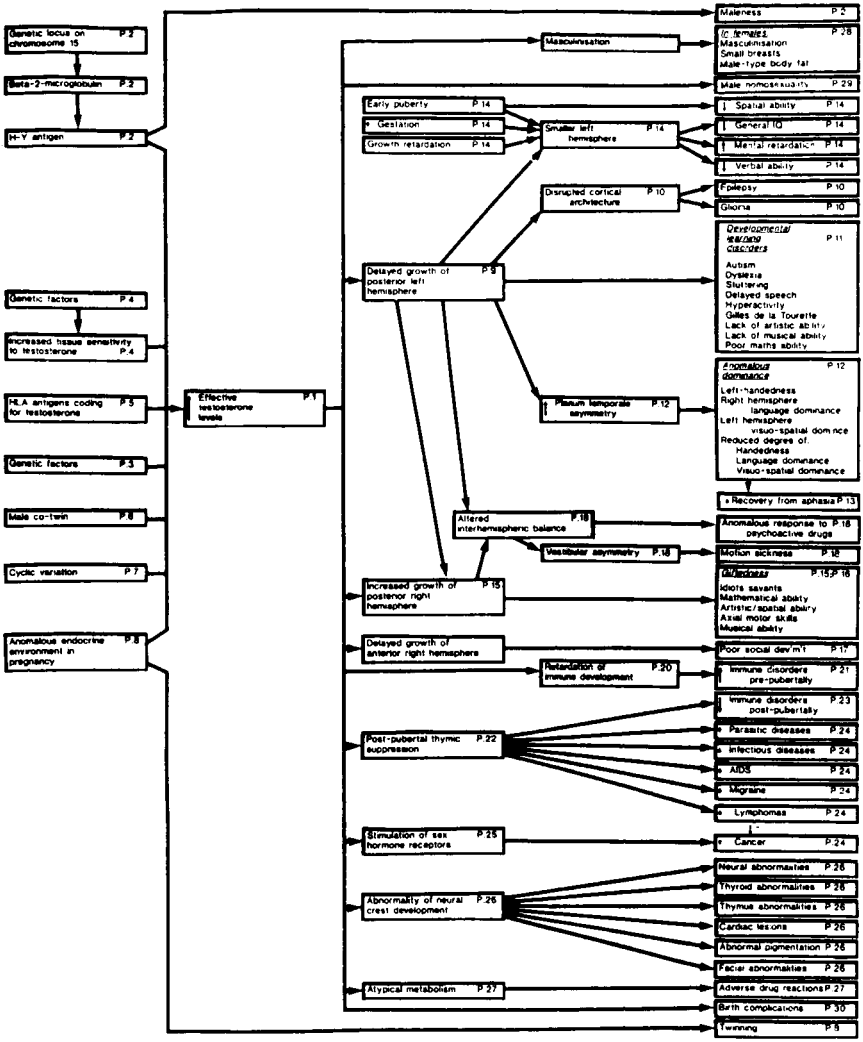

FIG. 1. A structural model of the Geschwind model of cerebral lateralization: Numbered references within boxes refer to the specific postulates identified in the original text. (From McManus & Bryden, 1991. Copyright 1991 by the American Psychological Association. Reprinted by permission of the publisher.)

system and leading to changes in the incidence of various immune diseases and to alterations in neural crest development, leading to cancer, neural crest disorders, and pigmentary changes.

At a very general level, then, the model predicts associations between 5 major categories of behavioral and biological variables: anomalous dominance, language development, intellectual abilities, immune disor-

ders, and neural crest disorders. In addition, the model predicts that there should be high intercorrelations within each of these 5 areas. Thus, there are 15 general topics in which one should find consistent relations among specific variables. Of these 15 sets of intercorrelations, 3 are primarily medical rather than psychological and will not be dealt with in any great depth in this paper: these are the associations within immune disorders and within neural crest disorders and the associations between immune and neural crest disorders. Of the remainder, 2 of the within-cluster sets of correlations, those within language disorders (cf. Bishop, 1990a) and those within intellectual abilities (cf. Sternberg, 1985) represent major domains of psychological research about which much has already been written and are far too broad in scope to deal with here. This leaves 10 major clusters of associations relating anomalous dominance, immune disorders, and neural crest disorders. Since the associations between handedness or anomalous dominance and the other variables (immune disorders, neural crest disorders, and intellectual ability) are perhaps the most surprising of the effects noted by Geschwind and his colleagues, our focus in the paper will be on these relations.

We will divide these groups into "major associations" and "minor associations." The major associations consist principally of associations with immune functioning and neural crest disorders, and they are of central importance to the GBG theory since they are not predicted by any other theory, they had not previously been suggested in the literature, and they are difficult to explain by other mechanisms and therefore their a priori probability was low. If these associations are not convincingly shown to be present then the GBG theory has serious problems. In contrast, the "minor associations" are those that GBG can explain reasonably adequately, but that cannot in the same sense be taken as critical tests of the model, since they had previously been much discussed in the literature, their suspected existence was in part responsible for the formulation of the theory, there are other theories that have attempted to explain them, and their failure as associations have an impact on a range of theoretical positions, and not just on the GBG model.

As an initial step we shall examine the novel theoretical concept of "anomalous dominance," which is central to the GBG theory. Then we will consider the "major associations," in particular considering anomalous dominance and immune disorders and specific language disabilities and giftedness, and the association of neural crest development with language disorders and immune deficits. In each of these sections we have attempted to be comprehensive in our citation of relevant evidence; that some sections are relatively short reflects the paucity of the evidence, rather than selectivity on our part. The section on "minor associations," which looks at the associations of anomalous dominance with language disorders, as well as with autism and Tourette syndrome, giftedness, and

spatial and verbal ability in the normal range, and with associations of testosterone levels with a range of phenomena, cannot pretend to be comprehensive, since some sections would require an extensive analysis to do justice to the breadth of the literature and have in any case been well reviewed in recent years; here, we attempt merely to give the flavor of the arguments and to come to a conclusion relative to the GBG theory alone.

THE CONCEPT OF ANOMALOUS DOMINANCE

Perhaps the most central neuropsychological concept in the GBG model is that of "anomalous dominance." Geschwind and Galaburda (1987) state that the majority of the population exhibit what they term the *standard dominance pattern.* This involves strong left hemisphere dominance for language and handedness and strong right hemisphere dominance for "other functions" (presumably such things as musical, visuospatial, and emotional processing). They then define AD as referring "to those in whom the pattern differs from the standard form" (p. 70).

This definition of AD raises two major issues. First of all, it assumes that handedness and the lateralization of language and visuospatial functions are related to one another, although perhaps in a complex way. Second, the definition leaves open to question just what should be considered "anomalous"; to what extent are minor signs of left-handedness, right-hemisphere language, or left-hemisphere visuospatial processing indicative of an anomalous state?

The extent of the problem can be seen by comparing the definitions of anomalous dominance in three separate studies. The study of Schachter, Ransil, and Geschwind (1987) defined anomalous dominance based on a questionnaire as a laterality index of <70 (where the index is in the range -100 to $+100$). The study of Chengappa, Ganguli, Yang, Schurin, Cochran, Brar, and Rabin (1992) included as AD subjects who were left-handed or left-eyed or left-footed. The study of Casey and Nuttall (1990) defined AD as being left-handed or ambidextrous (laterality index ≤ 40) or having at least one non-right-handed first degree relative. Taken together the lessons of these three studies seem to be that AD as used empirically is poorly defined, is highly fluid in its conceptualization, and can in principle include any of a wide range of measures (which potentially raises problems concerned with type I errors). The empirical problem also arises, as pointed out by Casey and Nuttall (1990), that a "substantial" proportion of the population will be defined as AD, even on their criteria; if a criterion of ≤ 70, along with left-eyedness, or left-footedness, etc., had been used then the incidence would be higher still.

The majority of tests of the GBG hypothesis employ handedness as a measure of AD, presumably because it is easy to measure in large sam-

ples. However, if the concept of AD is to be something more than another term for handedness, then it must include some separate and distinct contribution from language and visuospatial processes. At the same time, the GBG model implies that all of these are related, since they all have their origin in a common source, the level of fetal testosterone.

Furthermore, it makes a major difference to the model whether these factors are additive or interactive. By one view, AD is a graded characteristic and the more markers that are present, the more "anomalous" one is. By this view, those individuals with weak but normal lateralization on one factor and normal lateralization on the other two would be the individuals with the least degree of AD, while people with reversed dominance (strongly left-handed, right-hemisphere speech dominant and left-hemisphere dominant for nonverbal tasks) would show the greatest degree of AD. Such a view would imply that AD could be predicted by a linear combination of measures of handedness, language lateralization, and visuospatial lateralization. If this is the case, any one of the three critical variables will correlate with the factors relevant to AD, albeit not as well as the combined predictors.

On the other hand, AD is often treated as a dichotomous state such that one is either anomalous in one's dominance or is not. Such a view would consider all the anomalous states to be equivalent, so that anything other than the standard dominance pattern is "anomalous." This view implies a disjunctive relationship between handedness, language lateralization, and visuospatial lateralization in determining AD and would suggest that one could not adequately measure the concept without knowing something about all three variables.

It has long been known that handedness is related to language lateralization, but is far from a perfect predictor of it. In general, right-handers only very rarely have language functions lateralized to the right hemisphere, while such a state is far more common in left-handers. Nevertheless, the majority of left-handers, like right-handers, have language lateralized to the left hemisphere. There have been a number of large-scale surveys of the aphasia literature (e.g., Carter, Satz, & Hohenegger, 1984; Segalowitz & Bryden, 1983) and other attempts to study the relation between handedness and physiologically determined language lateralization (e.g., Rasmussen & Milner, 1977). In general, these studies show only a modest positive association between handedness and language lateralization, in that left handers are somewhat less likely to show left-hemisphere language lateralization. In addition, a number of behavioral measures have been employed to assess language laterality, such as the dichotic listening procedure. Bryden (1988b) has surveyed a large number of studies relating the dichotic right-ear advantage (REA) to handedness; his data show a significant positive association between handedness and verbal dichotic lateralization, but one that yields a phi coefficient of only

about +0.18. Certainly handedness cannot be used as a surrogate for language lateralization, as the two variables are only moderately associated.

Clinical data linking the right hemispheric representation of spatial function to handedness are somewhat more difficult to come by, but the data of Bryden, Hécaen, and DeAgostini (1983) suggest that there is relatively little difference between right-handers and left-handers in the representation of spatial functions

Studies of normal populations, using such techniques as dichotic listening or lateralized tachistoscopic presentation to assess the functions of the two cerebral hemispheres, are no more encouraging. While it is true, in general, that left-handers are less likely to show an REA for dichotically presented verbal material (see Bryden, 1988b for a review) and less likely to show a right visual field (RVF) superiority in visual half-field studies (see Annett, 1982, for a review), studies of handedness effects with nonverbal tasks are less common and less compelling in detecting a difference between handedness groups (e.g., Bryden, Free, Gagné, & Groff, 1991; McGlone & Davidson, 1973; Sheehan & Smith, 1986). Sheehan and Smith (1986), for example, used both dot enumeration and consonant–vowel–consonant identification as visual field tasks, in consistent and inconsistent left- and right-handers. While there were larger visual field effects for consistent-handers than for inconsistent-handers, there was no main effect of handedness. In these data, degree and not direction of hand preference proved to be the relevant variable. Other studies of dot detection or enumeration have failed to find significant differences between left-handers and right-handers (e.g., Bryden, 1973; Haude, Morrow-Tlucak, Fox, & Pickard, 1987). In contrast, studies of laterality effects in face recognition have consistently shown a stronger left visual field advantage in right-handers (David, 1989; Gilbert, 1977; Kim, Levine, & Kertesz, 1990; Piazza, 1980).

Studies attempting to correlate verbal and nonverbal laterality effects are also not very encouraging. While the Sheehan and Smith (1986) study did find a negative correlation between verbal and nonverbal laterality effects within handedness groups, findings of no correlation (e.g., Alter, Rein, & Toro, 1989; Bulman-Fleming & Bryden, 1994; Bryden & MacRae, 1988; Kim & Levine, 1991; Ley & Bryden, 1982; Segalowitz & Plantery, 1985) or even positive ones (e.g., Efron, Koss, & Yund, 1983; Sidtis, 1982) are common. In factor analytic studies, Boles (1989, 1991, 1992) has found that verbal and nonverbal effects often load on distinct factors, rather than showing the reciprocal relationship demanded by the GBG model.

In summary, then, the data suggest that handedness and language lateralization are only modestly correlated. The data on the relation of handedness to putative right-hemisphere functions are inconsistent, but sug-

gest not only that visuospatial functions are relatively independent of handedness and language, but also that different right-hemisphere processes may relate to handedness in different ways. In any event, adding "anomalies" of right-hemisphere function to the definition of "anomalous dominance" would seem to muddy the issue rather than clarify it.

A further problem lies in determining just who is "anomalous." As a simple notation, let us represent the lateralization of various functions by a triplet of the two letters L and R (representing left and right representation, respectively) in the form: handedness, language, nonverbal, using lowercase letters to indicate weak lateralization and upper case letters to indicate strong lateralization. By this convention, standard dominance can be represented as RLR (right-handed, left-hemisphere language, right hemisphere for nonverbal function). Deviations from this, such as LLR, RRR, RLL, LRR, LLL, RRL, and LRL all represent various forms of AD. Since GBG make it clear that the AD group includes those with "various degrees of deviance from the more uniform pattern of the larger group with standard dominance" (p. 71), such patterns as rlr, rLr, rlR, RLr, RLr, and rLR also must be considered to represent cases of AD: in other words, 63 of the 64 possible patterns are "anomalous."

While the number of anomalous patterns may not be critical, there are two great dangers in accepting any deviation from the RLR pattern as "anomalous." First, we run the risk of defining the majority of the population as being "anomalous." The proportion of individuals expected to show anomalous dominance will depend on the proportions considered "anomalous" on each of the three variables and on the intercorrelations between the variables, as indicated in Table 2. Schachter et al.'s (1987)

TABLE 2
Minimum and Maximum Possible Values for the Percentage of the Population Considered as Having "Anomalous Dominance" on Three Variables, and Overall

	Variables		
	Handedness	Lateralization of language	Lateralization of nonverbal functions
Minimum	8	9	10
Maximum	30	16	40

Overall Percentages of Anomalous Dominance

	Variables independent	Variables perfectly correlated
Minimum	25	10
Maximum	65	40

choice of +70 as a cutoff point on the Edinburgh Handedness Inventory results in some 30% of the population being classified as "non-right-handed," and therefore "anomalous." This value might be considered the maximum value for the percentage of the population exhibiting anomalies of handedness (see Table 2). As a minimum, about 8% (the truly left-handed) are anomalous on this dimension. While the best estimates of language representation suggest that no more than 9% of the population manifest right-hemisphere or bilateral language representation (Rasmussen & Milner, 1977; Segalowitz & Bryden, 1983), if we add those with "weak" left-hemisphere lateralization, however that might be measured, we at least double this figure (e.g., Snyder, Novelly, & Harris, 1990). Visuospatial functions, however, are not so clearly lateralized to the right hemisphere; at the very least, the percentage of people with left-hemisphere visuospatial functions is somewhat greater than that for right-hemisphere language, and we have arbitrarily selected a figure of 10%. At the other extreme, the data of Bryden et al. (1983) suggest that as much as 40% of the population has some left-hemisphere or bilateral involvement in visuospatial processing. If the proportions of anomalous dominance on three measures are a_1, a_2, a_3, then, if the measures are perfectly correlated, the overall incidence of anomalous dominance is max (a_1; a_2; a_3); alternatively, if the measures are statistically independent, then the incidence of AD is $1 - [(1-a_1)(1-a_2)(1-a_3)]$. Thus, as Table 2 shows, the likelihood of anomalous dominance is at least 20% and may reach 61% even with relatively conservative definitions of anomaly.

A second point is that an asymmetric division into "strong right-handers" and "non-right-handers" is necessarily arbitrary. Such a division presumes that there is an underlying continuum running from strongly right-handed to strongly left-handed, such that one can divide the distribution at any point and make meaningful statements. Bishop (1990c) has shown very clearly that one can grossly overestimate significance levels for the association between handedness and other variables by arbitrarily selecting the point at which one divides the group into "right-handers" and "non-right-handers." Including weak right-handers with left-handers also denies the possibility that degree of lateralization and direction of lateralization may be quite separately determined. Collins (1977, 1985) and Bianki (1988) have shown, in mice, that one can select for degree of paw preference but not for direction, indicating that the two are determined by separate mechanisms. Likewise, Bryden (1987) found that the heritability of degree of handedness was greater than that for the direction of handedness in a three-generational study of human handedness, although McManus (1985) reported that while direction of handedness ran in families, degree of handedness showed no significant parent–offspring correlation. In children, McManus, Sik, Cole, Mellon, Wong, and Kloss (1988) have argued that degree of lateralization

is a matter of training and experience, while direction is more likely to be biologically determined. To the extent that degree and direction of handedness (or any form of cerebral lateralization) are separately determined, a division into strong right-handers versus others inextricably confounds the two: one is comparing a group of people who are right-handed and also strongly handed to a second group that is both less likely to be right-handed and also less likely to be strongly handed.

The conceptualization of handedness as a continuum and the consequent division into "clear right-handers" and "non-right-handers" also carries with it the implication that all left-handedness is somehow pathological, representing varying degrees of deviation from a purely right-handed norm. That is, in order to justify an arbitrary division into "right-handers" and "non-right-handers," one must imagine a continuum with an origin at one end of the scale rather than in the middle of it. If "pure right-handedness" represents some kind of biological norm, then increasing deviations from this can be conceptualized along a continuum, with weak right-handedness representing a moderate deviation, weak left-handedness a somewhat greater deviation, and strong left-handedness the most extreme deviation. In contrast, if one views handedness as a characteristic that may develop normally from an initial undifferentiated state to either extreme right-handedness or extreme left-handedness, then the conceptual origin of the handedness continuum is at zero—neither left-handedness nor right-handedness—and degree and direction of handedness become quite different concepts.

Of course, similar arguments apply to the conceptualization of other functional asymmetries. Language functions, for example, are often bilaterally represented in the brain (Rasmussen & Milner, 1977; Loring, Meador, Lee, Murro, Smith, Flanigin, Gallagher, & King, 1990; but see Snyder et al., 1990). It is important to distinguish between a pathological conception of right-hemisphere language, in which bilateral representation is a moderate deviation from the left-hemisphere norm and right-hemisphere representation is a more extreme deviation, and an ontogenetic view in which unilateral representation, whether left or right, is the developmental norm, and bilateral representation represents a failure of those processes that lead to normal lateralization. In the first case, one would predict that language functions would be maximally altered in cases of right-hemisphere language, while in the latter event one would expect that language functions would be maximally altered in cases of bilateral language. In general, we take the position that handedness, language lateralization, and visuospatial lateralization are best conceptualized as being deviations of degree and direction from a symmetric null state. In our opinion, this view carries with it less conceptual baggage.

The final problem with the concept of AD is a statistical and methodological one. AD is not itself a measured variable, but is instead a theoret-

ical reclassification, defined in terms of a number of separate items—handedness, language lateralization, nonverbal lateralization, etc.—each of which is directly measurable and is dichotomous. Conceptualizing the situation in terms of ANOVA, the logical basis for the concept of AD is that certain dependent variables cannot adequately be modeled in terms of main effects of the measured dichotomous independent variables and that instead interaction terms are required among those independent variables, such that the inclusion of the interaction terms produces a significantly better fit to the data. Although AD can therefore only obtain its theoretical justification by the empirical demonstration that interaction terms produce an improvement in model fit, that demonstration has never been made by GBG. Occam's razor can therefore be invoked to argue that AD is an unnecessarily complex description of the phenomena and that until its proponents have demonstrated that it is indeed a better description of the data by showing the need for such interaction terms, then it is without formal justification.

As an initial problem with the GBG model, then, we would argue that AD is poorly defined and a difficult concept with which to work. While language dominance and handedness are certainly related to one another, right-hemisphere function is not closely linked to either of them. Thus, one runs the risk of defining virtually everyone as "anomalous" in some way. Until we better understand the functions of the right hemisphere, it would perhaps be better to encompass only handedness and language in the concept of AD. Even then, as we have indicated above, it remains unclear which deviations from pure right-handedness and complete left-hemisphere lateralization for language should be accepted as "anomalous." If AD is to have any theoretical utility as a concept then it must be strictly defined; otherwise, it will end up like the loose, ill-defined group of conditions that became known as "latent left-handedness" (Luria, 1970), in which the presence of a wide variety of lateralized anatomical and behavioral markers was used as an explanation of any pattern of atypical language dominance.

Major Associations

Anomalous Dominance and Immune Disorders

Geschwind and Behan (1982) reported the very provocative finding of an association between autoimmune disorders and left-handedness. In two surveys carried out in London and Glasgow, they found that strongly left-handed individuals and their first- and second-degree relatives were more likely to suffer from various immune disorders than strongly right-handed people and their relatives. In addition, left-handers also reported a higher incidence of learning disorders such as developmental dyslexia and stuttering. In this survey, immune disorders included celiac disease,

dermatomyositis, diabetes, Hashimoto's thyroiditis, myxedema, Crohn's disease, rheumatoid arthritis, thyrotoxicosis, ulcerative colitis, and uveitis. In a second study reported in the same paper, they found a greater incidence of left-handedness in patient populations with severe migraine or myasthenia gravis, but not in patients with rheumatoid arthritis, multiple sclerosis, or mixed-collagen vascular diseases. In a subsequent study, the same authors (Geschwind & Behan, 1984) reported higher incidence of migraine, allergies, dyslexia, stuttering, skeletal malformations, and thyroid disorders in left-handers. They also reported an elevated incidence of left-handedness in patients with Crohn's disease, celiac disease, thyroid disorders, and ulcerative colitis and, by employing a one-tailed test of significance, in those with myasthenia gravis.

Studies intended to replicate these findings have used a variety of different approaches and have met with mixed success. Several authors have carried out large-scale surveys of individuals unselected for the presence of immune disorders, often using undergraduate classes (e.g., McKeever & Rich, 1990; Van Strien, Bouma, & Bakker, 1987). Using such an approach, van Strein et al. (1987) found no increase in allergies, migraine, or various autoimmune diseases among left-handers in a large Dutch sample. Likewise, Bishop (1986) found no increase in the incidence of allergies, eczema, psoriasis, or asthma in a very large sample. Fry (1990) found no significant differences between right- and left-handers in the incidence of allergies, although allergies were more common in strongly left-handed individuals than in strongly right-handed ones. While McKeever and Rich (1990) found very few significant effects, their data showed a slightly elevated incidence of left-handedness in women who had been treated for immune disorders. Since the Geschwind argument (Geschwind & Galaburda, 1987) related handedness to immune disorders through an elevation of fetal testosterone, the fact that the McKeever and Rich (1990) effects are confined to women provides evidence against the details of the Geschwind hypothesis. In a group of elderly subjects, Burke, Yeo, Vranes, Garry, and Goodwin (1988) assessed immune antibodies and found a significant correlation between the presence of handedness and the report of developmental language disorders, but no correlation between immune disorders and handedness. Daniel, Thoma, Shaw, Yeo, Gangestad, and Korthank (1993) did find that left-handed undergraduates reported a longer duration of illness for minor infections such as colds and sore throats, but these effects were not specifically related to immune disorders. In a study of musical talent, Hassler and Gupta (1993) found that the level of IgE (an index of the body's immune response) was elevated in those showing either no right-ear advantage or a left-ear advantage in dichotic listening and that left-handed males, but not females, showed a moderately higher incidence of putatively immune disorders.

Other researchers have selected clinic-based samples of people with specific diseases and compared these to control subjects. Such a method, of course, is limited by the adequacy of the control sample employed. The data from such patient populations are equivocal, with some studies finding positive effects and others not. Smith (1987), for instance, found a higher incidence of left-handedness in patients at an allergy clinic. The incidence of left-handedness in patients with eczema or urticaria, or with IgE-mediated allergies, was particularly high. Similarly, Lelong, Thelliez, and Thelliez (1986) reported a much elevated incidence of left-handedness in allergy patients. Weinstein and Pieper (1988) reported an increased incidence of left-handedness in patients from an allergy practice and a health screening clinic. Left-handedness was significantly more common in those with hay fever, but not in those with asthma. Curiously, the significant handedness effect was lost when the analysis was restricted to those with positive skin tests, suggesting that the increase in left-handedness may be attributable to those who imagine themselves to be allergic and see a physician, rather than to those who are actually allergic (cf. Chavance, Dellatolas, Bousser, Amor, Grardel, Kahan, Kahn LeFloch, & Tchobroutsky, 1990).

In contrast, Betancur, Vélez, Cabanieu, LeMoal, and Neveu (1990) found no overall association between handedness and allergies, although they did report that the incidence of left-handedness was elevated in those whose allergic symptoms appeared prior to puberty. Among patients with ulcerative colitis or Crohn's disease, Searleman and Fugagli (1987) found an increased incidence of left-handedness, although such an effect was not observed by Meyers and Janowitz (1985). While some researchers have found an increased incidence of left-handedness in patients with systemic lupus erythematosus (Chavance et al., 1990; Lahita, 1988), this was not observed by Schur (1986). Furthermore, Denburg (1992) has found that 8% of lupus patients are left-handed; while her study lacks control data, the figure is not obviously higher than that found in the general population. In patients with myasthenia gravis, Cosi, Citterio, and Pasquino (1988) reported a trend toward a reduced, rather than an elevated, incidence of left-handedness, a finding which has subsequently been replicated by McManus, Naylor, and Booker (1990). Bear, Agostini, and Saporta (1988) have reported that frontal cerebral asymmetry, normally greater on the right, is reversed in patients with AIDS. However, while some studies have reported an increased incidence of left-handedness in AIDS patients (Becker, Bass, Dew, Kingsley, Selnes, & Sheridan, 1992), others have failed to find evidence of such an effect (Marchant-Haycox et al., 1991; Satz, Miller, Selnes, Van Gorp, D'Elia, & Visscher, 1991). In children with migraine, Guidetti, Moschetta, Ottaviano, Seri, and Fornara (1987) have claimed an increased incidence of ambilaterality or "random" handedness. Investigating a broad range of

immune disorders in a large outpatient sample, Berge and Segalowitz (1992) found no associations with handedness. Finally, Searleman and Fugagli (1987) have suggested a possible sex-dependency, in that males with type 1 diabetes (insulin-dependent) were more likely to be left-handed than those with type 2 diabetes (non-insulin-dependent), while the same did not hold for females. Chavance et al. (1990), however, found no effect of type 1 diabetes on handedness, although they did not examine sex effects carefully.

A further approach (cf. McManus & Bryden, 1991) is to investigate the relation between immune disorders in one group and handedness in their first-order relatives. Thus, Fry (1990) has reported that the offspring of left-handed mothers are more likely to have allergies than are the children of right-handed mothers. A similar effect did not appear for the children of left-handed fathers. Weinstein, Gurvitz, Greenberg, Weinstein, Solomon, Subbaiah, and Pieper (1992) reported that asthmatic women have a higher proportion of left-handed children than do nonasthmatics. Curiously, they also appear to have more children (an average of 2.21 children for 139 asthmatics, as opposed to an average of 1.90 children for 387 nonasthmatics).

In a preliminary analysis of the published data on handedness and immune disorder, Bryden and McManus (1992b) found that the data for many disease categories were either inconsistent or showed no significant relation to handedness. However, they suggested that several diseases, such as migraine, colitis, and thyroiditis, did appear to be consistently more common in left-handers. Most interestingly, several diseases actually appeared to be less common in left-handers (eczema, urticaria, and myasthenia gravis).

A meta-analysis. To explore better the relation between handedness and immune disorders, we searched the literature for papers reporting associations between handedness and conditions that either have a clear immunological origin, or are putatively immune in origin (including for instance migraine, on the basis that Geschwind and Behan argued for its immunological origins). In order to assess the reliability of the findings, we investigated only those conditions that had been studied by at least two separate sets of workers. On this basis, we considered a total of 89 separate sets of data that compared cases with controls, derived from 25 published studies and 1 unpublished data set (see Table 3), and referring to 14 different conditions (see Table 4). We included in our meta-analysis all published data sets of which we were aware. The data of Fry (1990) could not be included in the formal analysis since the original paper contains an insufficient statistical description, stating only that the association between allergies and left-handedness was nonsignificant. We made no systematic attempt to find unpublished studies and included only the unpublished study by Rovet (1993) of which we became aware. That

TABLE 3.

Summarizes Studies Which Have Assessed the Relationship between Handedness and Various Conditions, Studies Being Included if There Are at Least Two Separate Studies for That Condition. Significance of Individual Studies Is Assessed Using a Pearson χ^2 without Yates' Correction

Study	Description	Condition	Cases		Controls		Significance
			% Left	*N*	% Left	*N*	
Betancur, Vélez, Cabanieu, LeMoal, and Neveu (1990)	Allergy clinic population; patient controls with no history of allergy; modified Edinburgh Handedness Inventory[a]	Allergies	9.54%	325	9.35%	139	NS
Berge and Segalowitz (1992)	Patient and control population from general practitioners' offices; modified Edinburgh Handedness Inventory (9 items)	Immune disorders	8.52%	176	7.21%	111	NS
Bishop (1986)	National Child Development Study of all births in a national cohort; controls free of all conditions; handedness assessed from the square-marking task and collapsed into two categories with mixed-handers scored as left-handed[b]	Allergies	15.57%	1015	15.17%	11535	NS
		Asthma	16.11%	329	15.17%	11535	NS
		Diabetes type I[c]	26.32%	19	15.17%	11535	NS
		Eczema	13.10%	756	15.17%	11535	NS
		Migraine	19.05%	21	15.17%	11535	NS
		Psoriasis	13.24%	136	15.17%	11535	NS
Bryden, McManus, and Steenhuis (1991)	College students asked about a range of conditions; controls do not have that particular condition; handedness assessed by 25-item questionnaire	Any allergies	6.15%	130	10.13%	612	NS
		Asthma	11.63%	43	9.30%	699	NS
		Eczema	8.00%	50	9.54%	692	NS
		Hay Fever	10.65%	169	9.08%	573	NS
		Migraine	12.07%	58	9.21%	684	NS
		Arthritis[d]	6.67%	15	9.49%	727	NS

Chavance, Dellatolas, Bousser, Amor, Grardel, Kahan, Kahn, LeFloch, and Tchobroutsky (1990)	Hospital clinic population; controls randomly sampled from a community and reporting no allergic conditions; 10-item handedness questionnaire	Diabetes type I	5.00%	220	4.85%	165	NS
		Thyroid disease[e]	8.51%	47	4.85%	165	NS
		SLE or polymyositis	10.45%	134	4.85%	165	NS
		Migraine	6.88%	218	4.85%	165	NS
		Allergies[f]	8.29%	567	4.85%	165	NS
Cosi, Citterio, and Pasquino (1988)	Clinic population; controls were hospital personnel; modified Edinburgh Handedness Inventory	Myasthenia gravis	0.98%	102	6.18%	178	$p < .05$
Dellatolas, Annesi, Jallon, Chavance, and Lellouch (1990)	Study 1: Students, nurses and hospital employees asked about a range of conditions; controls do not have that particular condition; 10-item handedness questionnaire	Asthma	8.70%	46	11.50%	652	NS
		Eczema	4.00%	50	11.88%	648	NS
		Hay fever	12.50%	112	11.09%	586	NS
		Urticaria	8.99%	89	11.66%	609	NS
Dellatolas, Annesi, Jallon, Chavance, and Lellouch (1990)	Study 2: Male French army recruits asked about a range of conditions; controls do not have that particular condition; 12-item handedness questionnaire	Allergies	10.64%	1786	11.61%	6873	NS
		Asthma	14.11%	581	11.22%	8078	$p < .05$
		Eczema	10.59%	746	11.49%	7913	NS
		Hay fever	11.90%	1471	11.31%	7188	NS
		Urticaria	11.22%	1452	11.45%	7207	NS
Geschwind and Behan (1982)	Study 1, Part 1: Strongly left-handed subjects visiting a shop for left-handers in London; controls from general population of Glasgow matched for age and sex; handedness measured using Edinburgh Handedness Inventory. Subjects included only if had extreme scores	Immune disorders	72.97%	37	48.19%	469	$p < .005$

TABLE 3—*Continued*

Study	Description	Condition	Cases		Controls		Significance
			% Left	*N*	% Left	*N*	
Geschwind and Behan (1982)	Study 1, Part 2: Subjects from general population of Glasgow; immune disorder classified only if diagnosed at teaching hospital; handedness measured using Edinburgh Handedness Inventory	Immune disorders	46.43%	28	27.02%	866	$p < .05$
Geschwind and Behan (1982)	Study 2: Hospital-treated patients with condition; controls from general population of Glasgow "selected by the same methods as those described in the first study"; handedness measured using Edinburgh Handedness Inventory	Migraine	11.64%	146	7.18%	1142	NS
		Myasthenia gravis	13.27%	98	7.18%	1142	$p < .05$
Geschwind and Behan (1984)	Strongly left-handed subjects in Scotland or visiting a shop for left-handers in London: controls from general population of Scotland; handedness classified from extreme scores on Edinburgh Handedness Inventory	Allergies	88.57%	35	38.69%	1057	$p < .001$
		Migraine	58.93%	112	38.16%	980	$p < .001$
		Thyroid disorders	65.00%	20	39.83%	1072	$p < .05$

Geschwind and Behan (1984)	Patients with autoimmune disease; controls; handedness assessed by the Edinburgh Handedness Inventory	Ulcerative colitis or Crohn's disease	27.42%	62	10.60%	1000	$p < .001$
		Diabetes[g]	20.00%	20	10.60%	1000	NS
		Myasthenia gravis	19.44%	36	10.60%	1000	NS
		SLE or polymyositis	10.00%	30	10.60%	1000	NS
		Arthritis[h]	13.75%	80	10.60%	1000	NS
		Thyroid disorders	22.50%	40	10.60%	1000	$p < .05$
Lahita (1988)	Clinic population; controls are normal and clinic volunteers; Edinburgh Handedness Inventory	SLE or polymyositis	15.67%	134	10.69%	608	NS
Lelong, Thelliez, and Thelliez (1986)	Clinic population of children with allergy to mites; controls from local school. Non-right-handedness assessed as left- and mixed-handers	Allergies	24.32%	625	11.12%	403	$p < .001$
Marchant-Haycox, McManus, and Wilson (1991)	Nonclinic population of homosexuals and heterosexuals; controls were those without a particular condition; 9-item handedness questionnaire	Arthritis	8.33%	60	9.59%	730	NS
		Migraine	7.32%	164	10.06%	626	NS
		Thyroid disorder	7.14%	14	9.54%	776	NS
		Eczema	8.93%	112	9.59%	678	NS
		Psoriasis	10.00%	50	9.46%	740	NS
McKeever and Rich (1990)	Student population, condition included if treated for it or diagnosed by doctor as having it; controls from same population who did not have that particular disease; handedness classified from writing hand	Allergies	12.04%	540	10.71%	2540	NS
		Asthma	10.45%	220	10.98%	2860	NS
		Colitis	0.00%	4	10.96%	3076	NS
		Diabetes type I	0.00%	5	10.96%	3075	NS
		Eczema	17.11%	76	10.79%	3004	NS
		Hay fever	9.62%	260	11.06%	2820	NS
		Migraine	14.17%	120	10.81%	2960	NS
		Thyroid disorder	8.33%	12	10.95%	3068	NS

TABLE 3—*Continued*

Study	Description	Condition	Cases		Controls		Significance
			% Left	*N*	% Left	*N*	
McManus, Naylor, and Booker (1990)	Study 1: members of British Association of Myasthenics; spouse acted as control; LQ ≤ 0 on a 9-item handedness questionnaire	Myasthenia gravis	2.70%	74	9.46%	74	NS
McManus, Naylor, and Booker (1990)	Study 2: members of British Association of Myasthenics; same-sex, age-matched control; LQ ≤ 0 on a 9-item handedness questionnaire	Myasthenia gravis	4.00%	50	8.00%	50	NS
Meyers and Janowitz (1985)	Clinic population; controls are patients and hospital employees; Edinburgh Handedness Inventory	Ulcerative colitis or Crohn's disease	12.05%	83	12.31%	130	NS
J. Rovet (personal communication, Feb. 25, 1993)	Clinic population of children with diabetes; controls are siblings of cases	Type I diabetes	9.38%	64	7.14%	42	NS
	Clinic population of children with congenital hypothyroidism; controls are siblings of cases	Congenital hypothyroidism	12.74%	102	5.26%	57	NS
Salcedo, Spiegler, Gibson, and Magilavy (1985)	Clinic population; controls are parents of patients; handedness classified by writing and eating hand	SLE or polymyositis	14.81%	54	12.96%	108	NS

Satz, Miller, Selnes, Van Gorp, D'Elia, and Visscher (1991)	Male homosexual volunteers in the Multicentre AIDS cohort study; controls are subjects without allergies; handedness assessed by self-reported writing hand and by a 5-item inventory	Allergies	15.44%	395	11.87%	598	NS
Schur (1986)	Clinic population with SLE; normal controls matched for age and sex; handedness assessed by a modified Edinburgh Handedness Inventory	SLE or polymyositis	6.98%	86	14.17%	120	NS
Searleman and Fugagli (1987)	Members of National Foundation for Ileitis and Colitis and the American Diabetes Association; controls from a university town; 7-item handedness questionnaire	Ulcerative colitis or Crohn's disease	27.54%	207	12.64%	277	$p < .001$
		Diabetes type I	12.61%	119	12.64%	277	NS
Smith (1987)	All patients attending allergy clinic with a definite diagnosis (some patients have more than one diagnosis); controls collected at railway stations; Edinburgh Handedness Inventory	Asthma	14.44%	111	8.86%	350	NS
		Eczema	26.47%	34	8.86%	350	$p < .01$
		Hay fever	14.72%	163	8.86%	350	$p < .05$
		Urticaria	25.00%	48	8.86%	350	$p < .001$
Stanton, Feehan, Silva, and Sears (1991)	Dunedin Multidisciplinary Health and Development Study cohort at age 9; diagnoses made by pediatricians from parental history and examination; controls are	Eczema	5.62%	178	7.37%	597	NS
		Urticaria	4.48%	67	7.20%	708	NS
		Rhinitis	4.72%	128	7.41%	648	NS
		Asthma	5.41%	148	7.35%	626	NS

TABLE 3—*Continued*

Study	Description	Condition	Cases		Controls		Significance
			% Left	*N*	% Left	*N*	
	subjects without a particular condition; handedness assessed by the Harris Tests of Lateral Dominance at age 7; mixed-handers grouped with right-handers[i]						
Stanton, Feehan, Silva, and Sears (1991)	Dunedin Multidisciplinary Health and Development Study cohort at age 13; diagnoses made by pediatricians from history and examination; controls are subjects without a particular condition; handedness assessed by the Harris Tests of Lateral Dominance at age 7; mixed-handers grouped with right-handers	Eczema	1.50%	133	8.90%	573	$p < .01$
		Urticaria	5.36%	112	7.93%	593	NS
		Rhinitis	7.91%	215	7.33%	491	NS
		Asthma	8.50%	200	7.11%	506	NS
Steenhuis, Bryden, and Schroeder (1993)	Participants in career counseling program; controls are those without a particular condition; handedness as-	Allergies	15.93%	2686	14.17%	4567	$p < .05$
		Arthritis	11.74%	746	15.21%	6550	$p < .01$
		Diabetes type I	14.68%	109	14.85%	7187	NS
		Migraine	14.77%	1611	14.86%	5685	NS

	sessed by writing hand, with left and ambidextrous combined						
Van Strein, Bouma, and Bakker (1987)	Student population with separate recruitment of left- and right-handers; autoimmune data collected during second study; handedness assessed by writing hand	Allergies	67.47%	83	56.94%	144	NS
		Immune disorders	61.54%	13	60.75%	214	NS
		Migraine	65.96%	47	59.44%	180	NS
Weinstein and Pieper (1988)	Patients from an allergy clinic and a health screening clinic; controls are patients without a particular condition; handedness assessed using a modified Edinburgh Handedness Inventory	Allergies	10.80%	499	6.00%	267	$p < .05$
		Hay fever/rhinitis	11.20%	464	6.60%	302	$p < .05$
		Asthma	11.30%	159	8.40%	609	NS

[a] Also known as the Oldfield Handedness Questionnaire.

[b] Conditions were ranked from least common to most common, and subjects allocated to the *one* least common condition if they suffered from several conditions.

[c] "Diabetes" in original study; presumably type I from age of subjects.

[d] Questionnaire specifically asked about "rheumatoid arthritis."

[e] Study specifically asked about "Graves' disease" (thyrotoxicosis).

[f] Nonclinic, population-derived controls who reported any allergy ("dubious controls" as described by authors).

[g] Diabetes not specified as type I or II.

[h] Specifically recorded as "rheumatoid arthritis."

[i] The data for the two separate sweeps of the Stanton et al. studies consider the same subjects and therefore both data sets have been entered into the study, but with all values weighted by 0.5.

TABLE 4
Significance Testing by Multiple Logistic Regression of Studies Testing Association between Handedness (Dependent Variable) and Subjects with or without (Factor "Cases") the Various Conditions (Factor "Diseases")

	Without Geschwind data			With Geschwind data		
Component	Deviance	Change in deviance	Significance	Deviance	Change in deviance	Significance
Constant	**936.70** (151 *df*)	—	—	**2182.45** (177 *df*)	—	—
Study	116.77 (76 *df*)	819.93 (75 *df*)	$p << .001$	207.18 (89 *df*)	1975.27 (88 *df*)	$p << .001$
Cases	112.55 (75 *df*)	4.23 (1 *df*)	$p < .05$	189.22 (88 *df*)	17.95 (1 *df*)	$p < .001$
Cases × disease	79.41 (62 *df*)	33.14 (13 *df*)	$p < .0025$	144.87 (75 *df*)	44.35 (13 *df*)	$p < .001$
Cases × study within disease groups	0.00 (0 *df*)	79.41 (62 *df*)	NS	0.00 (0 *df*)	144.87 (75 *df*)	$p < .001$

Note. There were at least two studies for each of the fourteen different disease categories. The analysis was carried out separately with and without the original data which were reported by Geschwind and Behan.

study contributes only a small number of subjects, its omission produces no substantial change in any of the conclusions, and there is no evidence that its data are significantly discrepant from other studies.

The data generally come from two very different approaches: (a) studies in which a large population is surveyed and individuals are classified in terms of handedness and the presence or the absence of one or more conditions; the incidence of handedness and of immune condition therefore approximate population rates, so that right-handers and those without the condition predominate, and (b) studies in which subjects are selected either because they are left-handed or because they have a particular condition and then are assessed on the other measure; in such studies the incidence of left-handedness or of the condition is much higher than in population surveys. Despite the differences in marginal frequencies, the data from each type of study can be reduced to two incidences of left-handedness, one in subjects with the condition and the other in those without the condition, and the test of the GBG hypothesis is that left-handedness will be more common in those with the condition.

Statistical analysis was by means of a multiple logistic regression, with the incidence of left-handedness as the dependent variable and three independent variables. Statistical analysis was done using the program GLIM (see Healy, 1988, for an introduction). Each data set contributed 2 incidences of left-handedness (1 in cases and 1 in controls) and hence, there were 152 incidences derived from the 76 studies (excluding Geschwind & Behan, 1982, 1984). Variations of procedure among the different stud-

ies were accounted for by a factor STUDY with 76 levels (and hence 75 degrees of freedom), which accounted for overall differences in incidence of left-handedness. Nested within STUDY are 13 degrees of freedom corresponding to the 14 different DISEASE groups. A factor CASE, with two levels, compared cases with controls, accounting for the paired nature of the data, and tested the central question of whether the incidence of left-handedness differed in the cases and the controls.

A technical problem with the analysis concerns the nature of control subjects. In many studies, a single large set of subjects was asked about a number of different conditions. Those with the condition (a minority) were compared with those without the condition (the vast majority), who acted as controls. When comparing the various conditions, the controls are almost identical, although the cases are different in each comparison. Thus, if 1000 subjects are asked about two conditions and 50 subjects suffer from condition A and 20 suffer from condition B, then a maximum of 70 subjects indeed have the conditions, and at least 930 are healthy controls. The incidence of handedness of the 50 subjects with condition A can be compared with the handedness of the 950 who do not have condition A, and the handedness of the 20 subjects with condition B can be compared with the 980 subjects who do not have condition B, but that does not mean there are 950 + 980 = 1930 controls; there are somewhere between 950 and 980 controls. In such cases the specific controls for each condition (but not the cases) were weighted by a factor of $1/N$, in which N is the number of diseases studied (two in this case). Such weighting extracts the maximum information from cases without unjustifiably inflating the numbers of controls. Weighting was only used in the overall analysis of Table 4; the problem does not apply in examining the simple effects of Table 5, wherein cases are compared with controls consisting of all subjects in the study who did not have the condition.

A second technical problem concerns the manner in which one treats the data collected by Geschwind himself. At one level it can be argued that since these are legitimate data which have been collected in a similar manner to those in other studies then they should be included within the meta-analysis. However, there is also a counterargument that these data are necessarily special, having been used in part to generate the hypothesis, and therefore they cannot also be used to test it. An extreme view might be that the original data were merely the result of a type I statistical error. If so, then the strong prediction is that no further effects should be found in independent replications, and testing such a view requires the original data to be excluded from the meta-analysis. A second extreme view might be that, in any study, unconscious biases on the part of the investigators, particularly if they are concerned to collect evidence in favor of an interesting new theory, can distort the process of data collection. If that is the case then not only are those original data better

TABLE 5

The Association between Handedness and a Range of Immune Disorders, for Each of Which There Are at Least Two Studies in the Literature

Condition	Number of studies or independent data sets	Significance	Odds ratio	95% confidence interval	Heterogeneity
Any condition (excluding Geschwind and Behan studies)	76	$p < .05$	1.062	1.003–1.126	NS
Any condition (including Geschwind and Behan studies)	89	$p < .001$	1.128	1.076–1.181	<.001
Allergies	11	$p < .0025$	1.128	1.046–1.218	<.001
Arthritis (either rheumatoid or unspecified)	3	$p < .025$	.745	.594–.932	NS
Asthma	9	$p < .05$	1.184	1.004–1.351	NS
Diabetes type 1	6	NS	1.060	.753–1.491	NS
Eczema	9	NS	.875	.758–1.009	<.001
Hay fever or rhinitis	8	NS	1.097	.961–1.252	NS
Immune disorders (otherwise unspecified)	2	NS	1.135	.561–2.297	NS
Migraine	7	NS	1.027	.895–1.178	NS
Myasthenia gravis	3	$p < .01$	.267	.099–.722	NS
Psoriasis	2	NS	.892	.573–1.387	NS
Systemic lupus erythematosus or polymyositis	4	NS	1.288	.885–1.875	NS
Thyroid disorders	4	NS	1.533	.781–3.007	NS
Ulcerative colitis or Crohn's disease	3	$p < .001$	2.007	1.350–2.983	NS
Urticaria	5	NS	.986	.837–1.161	<.05

Note. Estimates in all cases exclude the data of Geschwind and Behan (1982, 1984), with the sole exception of that for "Any condition (including Geschwind and Behan studies)." "Any condition" analyses are weighted to take into account repeated use of a single control group, whereas estimates for individual conditions, which only have a single control group, are unweighted.

omitted from the process of meta-analysis, but the possibility of inconsistency with other investigators can be tested by comparing the original study with subsequent studies for significant effect size heterogeneities.

In the present analysis we therefore adopted the following strategy, which we believe is both statistically conservative and fair to the GBG hypothesis. First we would carry out a meta-analysis excluding the

Geschwind data, on the grounds that this is a conservative test of the original prediction and that appropriately significant results would strongly support the GBG hypotheses. Second, and particularly if the results of the first analysis were not compellingly in support of the theory, we would repeat the meta-analysis including the Geschwind data. If that analysis then produced compelling evidence in favor of the theory, we would nevertheless accept the result only if in addition there was no evidence suggesting significant heterogeneity between the Geschwind data and other data sets. If significant heterogeneity were present then we would instead take this as evidence that the Geschwind data should not be included in the analysis and base our conclusions on the data without the Geschwind studies. Finally, our analysis would explicitly search all those data sets studying a particular disease or condition for the presence of heterogeneity, and if significant heterogeneity were found, then we would take great care in basing conclusions on those data.

Table 4 summarizes the hierarchical model-fitting used in the analysis. Considering first the data excluding the Geschwind studies: at step 1, STUDY was added, to take account of differences in incidence of handedness among studies. This was massively significant ($p << .001$), not least because of the different study designs that were used. Addition of CASE (subjects with or without various DISEASEs) resulted in an improvement in fit which reached the .05 significance level ($\chi^2 = 4.23$, $df = 1$), meaning that overall there was some evidence that those with immune conditions were more likely to be left-handed; examination of the effect size (Table 5) shows that the odds ratio (OR) for left-handedness in cases as compared with controls was only distinguishable from unity at the third decimal place at its lower 95% confidence limit (LCL) (OR = 1.062, LCL = 1.003). The next step fitted the CASE × DISEASE interaction, which is relevant to whether the incidence of left-handedness differed in groups of conditions, and this term was highly significant ($p < .0025$), indicating that conditions differed in their association with left-handedness and which, in view of the barely significant effect of CASE, meant that some studies were associated with higher incidences of left-handedness and others with a lower incidence. Finally, the remaining variance, which is the interaction of CASE × STUDY within DISEASE groups, pertains to whether the studies are heterogeneous within the groups of conditions; this term is almost significant and suggests that when partitioned by disease there might be evidence for heterogeneity within some of the conditions.

The significant CASE × DISEASE interaction was analyzed as a series of simple effects by assessing the effect of CASE separately for each condition. Table 5 shows the OR and its 95% confidence interval for each condition; the OR is significantly greater than unity for allergies (OR = 1.128), asthma (OR = 1.184), and ulcerative colitis and Crohn's disease

(OR = 2.007) and significantly less than unity for arthritis (0.745) and myasthenia gravis (0.267). The problem of weighting of controls does not apply within DISEASE categories, since no study contributed non-independent controls, and therefore these analyses did not weight the control data as described earlier. The heterogeneity of effects within the fourteen conditions is also indicated in Table 5. Only three of the conditions show significant heterogeneity, and two of these (eczema: $\chi^2 = 26.18$, $df = 8$, $p < .001$; and urticaria (hives): $\chi^2 = 11.48$, $df = 4$, $p < .05$) are conditions for which no main effect is present. The third condition, allergies, shows a highly significant heterogeneity ($\chi^2 = 37.01$, $df = 10$, $p < .001$) and also shows a highly significant main effect between cases and controls. It is, however, one of the most diffusely defined of all the categories, and that may explain some of the undoubted variability among studies.

To summarize these findings, overall there is only marginal evidence that individuals with immune disorders are more likely to be left-handed than are controls, the 95% LCL for the effect being that cases are 1.003 times more likely to be left-handed than are controls. However, disorders are significantly heterogeneous, with three (allergies, asthma, and ulcerative colitis and Crohn's disease—considered as a single entity) having a *higher* incidence of left-handedness and two (arthritis and myasthenia gravis) having a *lower* incidence of left-handedness than controls. A "portmanteau" or "omnibus" test found little evidence for heterogeneity of findings among different studies within the disease groups, suggesting that the published literature is generally consistent in its results, although in the case of allergies there was very significant evidence for heterogeneity in effect size among studies.

Thus, this meta-analysis finds only marginal support for the GBG theory: left-handedness is only very slightly more frequent in individuals with putative immune disorders. Surprisingly, there is evidence that some diseases do show an increased incidence of sinistrality and others show a decreased incidence: we can see no clear pattern for these results and would feel more secure with the conclusion if there were additional replication with independent data. The existence of significant heterogeneity among studies for some conditions suggests that better definitional criteria should be used in future research and that methodological aspects of studies should be more carefully examined.

The meta-analysis reported here is a powerful one, being based on a total of 21,837 cases and a weighted total of 34,457 controls. Power analysis shows that for an alpha level of .05 and an incidence of left-handedness of 10% in the controls there is about a 90% probability of finding a significant difference in the rate of left-handedness in cases if they have an incidence of 10.84% (i.e., an 8.4% relative increase in incidence in cases as compared with controls; this is equivalent to an odds ratio of 1.094).

In the results reported so far, we have excluded the data reported originally by Geschwind and Behan (1982, 1984). To examine the effects of these data, we repeated the analysis, this time including their findings (see Tables 4 and 5). The effect of CASE now becomes highly significant ($p < .001$), with cases showing a higher incidence of left-handedness (OR = 1.128). The CASE × DISEASE interaction continues to be highly significant ($p < .001$). The most interesting change is that the CASE × STUDY within DISEASE interaction is now highly significant ($p < .001$) indicating the presence of heterogeneity within conditions. This heterogeneity should be interpreted as indicating that the Geschwind and Behan data are significantly discrepant from other data in the literature.

Anomalous Dominance and Immune Functioning

A more direct approach to the relationship between AD and immune functioning has been taken by Yokoyama, Hara, and Shiotsuki (1987), who compared peripheral lymphocyte subsets in 13 healthy left-handers and 14 healthy right-handers. They found evidence for an increased percentage of suppressor–inducer T cells in their left-handers. While this effect reached statistical significance, the effect was limited to 1 of 9 comparisons they carried out and hence is almost certainly not significant after taking multiple comparisons into account by a Bonferroni procedure. Thus, although this effect is interesting it cannot be seen as meeting conventional criteria for significance and cannot be treated as support for the GBG theory until larger samples provide independent replication.

Similarly, Chengappa, Cochran, Rabin, and Ganguli (1991) assessed healthy normal adults for the presence of circulating autoimmune antibodies and found an elevated incidence of autoantibodies in non-right-handers. Unfortunately, they assessed handedness by asking about the hand used for writing, the foot used for kicking, and the eye used for sighting through a tube and considered people to be "right-handed" only if they answered "right" to all of the questions. We have been able to examine the data (Chengappa, 1993) in more detail and wonder just what questions the participants were answering. In contrast to the general literature (e.g., Porac & Coren, 1981), virtually all of the right-handed subjects claimed to be right-eyed and most of the left-handed people claimed to be left-eyed. Because the variables of eye, hand, and foot preference are highly intercorrelated, it is virtually impossible to determine which is the most important. Furthermore, there is a highly significant race by sex interaction (with autoimmune antibodies more commonly found in black males and white females) that we are at a loss to explain. The handedness by antibody effect fails to reach significance in either blacks or whites when analyzed separately. Until these very unusual results are replicated independently, we feel that they cannot be seen as strong support for the GBG theory.

More recently, Chengappa et al. (1992) have reported that "non-right-sided" individuals, classified in the same way as in their earlier study, had significantly lower interleukin-2 production than did "right-sided" subjects. Interleukin-2 is considered to be important to the production of T lymphocytes and thus lower production of interleukin-2 may be a sign of immune deficiency. Again, however, these data do not permit us to determine whether eyedness, footedness, or handedness is the critical variable. Furthermore, at least one other study (Burke et al., 1988) has failed to find any correlation between handedness and the presence of immune antibodies. Nevertheless, the Chengappa group appears to have uncovered some important issues that need to be pursued in larger samples and with better laterality measures.

While links between the immune system and handedness may profitably be investigated by seeking to assay immune antibodies in otherwise healthy individuals, such research requires not only good immunological assays, but also careful measurement of lateralization effects. To date, researchers have failed to combine immunological and psychological precision.

Relations between the Immune System and Specific Language Disabilities

If the GBG model is correct in linking immune disorders to AD, then it follows that those who manifest developmental language disturbances should show increased evidence of altered immune function. The evidence supporting this position is tantalizing, to say the least.

For example, several studies provide some evidence that disorders of the immune system are more common in dyslexics, and perhaps in their immediate relatives as well, than in control cases. In surveying a large sample of dyslexic children, Hugdahl, Synnevåg, and Satz (1990) found that immune disorders were twice as common in these children as in the control sample. Likewise, Pennington, Smith, Kimberling, Green, and Haith (1987) reported a significant elevation of autoimmune and allergic disorders in a large sample of familial dyslexics, although there was no concomitant increase in the frequency of left-handedness. In contrast, Hynd, Semrud-Clikeman, Lorys, Novey, and Eliopulos (1990) and Obrzut and Atkinson (1993) found no elevation of immune disorders in dyslexics, although there was an increased incidence of left-handedness.

Rather than specifically targeting dyslexics, Burke et al. (1988) assessed immune antibodies in a group of elderly subjects. They found a significant correlation between the presence of immune disorders and the report of developmental language disorders, but no correlation between immune disorders and handedness. While one may question the validity of a self-report of developmental language disorder by an elderly subject,

there is no reason to believe that those with immune disorders would be more likely to remember childhood language difficulties than those without such disorders.

Galaburda, Sherman, Rosen, Aboitiz, and Geschwind (1985) autopsied four developmental dyslexics and found that all lacked the normal temporal planum asymmetry and all had either immune problems or indications of familial sinistrality. While there are no proper control data in this study, there is again an indication of increased immune difficulty in dyslexia.

The data are somewhat more ambiguous concerning the relatives of dyslexics. Gilger, Pennington, Green, Smith, and Smith (1992), reporting on four large family studies of reading disability, found an increased level of immune disorders in the relatives of reading-disabled subjects in only one of the studies. They concluded that an elevated incidence of immune disorder in the relatives of dyslexics was not a consistent or robust finding. However, Behan, Behan, and Geschwind (1985) have reported an elevated incidence of anti-Ro antibody in the mothers of dyslexics, although this rare antibody to small ribonucleoprotein particles was detected in only five of them. Urion (1988) was unable to find any difference in the incidence of immune disorders between the relatives of dyslexic boys and the relatives of control boys, although he did note that many of the members of families of those dyslexic boys who did manifest immune disorders also showed signs of premature greying.

A somewhat different approach is to examine the relatives of individuals with particular autoimmune diseases, rather than the relatives of dyslexics. Lahita (1988) found a very high incidence of dyslexia (44%) in the male offspring of women with systemic lupus erythematosus. Similarly, Hansen, Nerup, and Holbeck (1986) found an extremely high incidence of dyslexia in the relatives of patients with insulin-dependent diabetes. Curiously, the co-occurrence of both diabetes I and dyslexia was rare, leading the authors to suggest that dyslexia protected one against diabetes.

While there is little evidence on immune disorders in other developmental language disorders, among autistic children, Leboyer, Osherson, Nosten, and Roubertoux (1988) assert that there is evidence for increased food allergies and there was a suggestion of an increased incidence of celiac disease (Coleman, Landgrebe, & Landgrebe, 1976), although subsequent work (McCarthy & Coleman, 1979) has not verified this.

Gilles de la Tourette syndrome (TS) is a neurological disorder characterized by involuntary facial tics, vocalizations, coprolalia, and echolalia. Comings and Comings (1986) report that TS is associated with an elevated incidence of migraine. In a 1987 study (Comings & Comings, 1987), they report an elevated incidence of skin allergies associated with TS, but dismiss this as potentially being the consequence of self-induced skin

lesions. However, the incidence of rhinitis and allergies to pets is also increased in the TS sample, and 17.4% of their TS sample report asthma as opposed to 4.2% of their controls ($\chi^2 = 5.32$, $p < .05$). There is thus at least modest evidence for an increase in allergies in TS.

The bulk of the evidence, then, indicates that there is an elevated incidence of immune disorders in dyslexics and in those with developmental language disorders. There is at least reasonable evidence that this has some heritable basis, in that the relatives of people with some immune disorders show a high incidence of developmental language disorders. It is worth noting, however, that neither lupus (Lahita, 1988) nor diabetes (Hansen et al., 1986), the two disorders for which there is evidence for increased language difficulty in relatives of the afflicted, is related to handedness in our meta-analysis (Table 4).

Immune disorders and giftedness. The GBG model also predicts that immune disorders will be more prevalent in those who are highly talented, especially those who have well developed right-hemisphere functions, such as artists or musicians. In a continuing investigation of mathematically precocious children, Benbow and Benbow (1984) have reported that approximately 55% of intellectually precocious students scoring above 700 on the SAT-M or above 630 on the SAT-V had symptomatic atopic disease, in contrast to 35% of the low-scoring children and about 38% of the target subjects' parents and siblings. It is noteworthy that not only mathematically gifted subjects, but also verbally gifted ones, showed an increase in allergies, suggesting that there is no specific association with right-hemisphere function. In a study of the musically talented, Hassler and Gupta (1993) found a borderline trend for musically talented females to show higher levels of IgE, although this effect was reversed in males. Other than these studies, there seems to be little evidence on immune dysfunction in the gifted, and therefore no clear conclusions can be drawn.

Anomalous Dominance and Neural Crest Disorders

One of the more unexpected predictions of the GBG theory is that there are relations between AD and neural crest (NC) disorders of various types. Geschwind and Galaburda (1987) state specifically that AD or learning deficits should be related to disorders of the aortic arch and cardiac conduction system, to minor forms of otocephaly, facial hypoplasia, to scoliosis, to disorders of pigmentation, including eye and hair color, and premature greying, as well as facial naevi (pigmented and vascular) and Waardenburg syndrome. Additionally they refer to asymmetries of the normal skeleton and to associations of AD with Legg–Perthe's disease and with disorders of the vertebral column (e.g., Klippel–Feil syndrome and spina bifida). The authors also discuss

asymmetries in a range of other systems which seem to have little to do with the NC, such as in the sex organs (e.g., testes or the polycystic ovary syndrome), in skin, and in certain neoplasias (e.g., lymphomas, carcinomata of lung and breast, and lymphomata); they also relate certain sexual behaviors, such as masculinization or homosexuality, to atypical lateralization. The chapter finally concludes with a discussion of handedness in relation to hypertension, angina, and myocardial infarction. Here we will assume that they are only suggesting a relationship between AD and neural tube development in pages 156 to about page 168 and that the rest of the chapter consists principally of *miscellanea et esoterica*. Before reviewing the empirical evidence on these questions we must first overview the theoretical nature of the supposed association and examine current knowledge concerning the NC.

The neural crest. The NC was first described by Wilhelm His in 1868 (His, 1868), who described a band of cells in the embryonic chick lying between the neural tube on the one side and the future epidermal ectoderm on the other side, which he labeled the *Zwischenstrang*. The particularly intriguing aspect of the NC is that the cells rapidly migrate along highly precise channels to a vast range of locations within the developing fetus. Although the subject of controversy for many years, substantial amounts of experimental work in the past 50 years (much of it stimulated by the important work of Hoerstadius (1950) and the development of the method of using quail–chick chimeras by Le Douarin (1982) have meant that now it is fairly well understood, and the massive range of tissues to which it contributes has become better characterized. It is also clear that the NC is in evolutionary terms what Gans (1987) has called " a spectacular invention," being in large part responsible for the transition from the protochordates to the vertebrates. Current knowledge of the NC has been well reviewed in several recent volumes (Hall & Hoerstadius, 1988; Le Douarin, 1982; Maderson, 1987).

The vast range of tissues and organs to which the NC contributes is well illustrated by Hall and Hoerstadius (1988), who list the following cell types: sensory neurons, adrenergic neurons, satellite cells, glial cells, parafollicular cells, melanocytes, osteoblasts, osteocytes, fibroblasts, striated myoblasts, mesenchymal cells, angioblasts, cholinergic neurons, Rohon-Beard cells, Schwann cells, chromaffin cells, calcitonin-producing cells, chondroblasts, chondrocytes, odontoblasts, cardiac mesenchyme, smooth myoblasts, and adipocytes; among tissues or organs to which the NC contributes are listed spinal ganglia, sympathetic nervous system, thyroid gland, adrenal gland, craniofacial bone, dentine, adipose tissue, striated muscles, dermis, cornea, blood vessels, connective tissue of thyroid, parathyroid, thymus, pituitary and lachrymal glands, parasympathetic nervous system, peripheral nervous system, craniofacial cartilages, tooth papilla, connective tissue, smooth muscles, cardiac septa, eye, en-

dothelia, heart, and brain. Similar lists elsewhere (Bolande, 1974; Le Douarin, 1982) are equally extensive, and new involvements continue to be reported, such as in the stria vascularis of the inner ear (Steel & Barkway, 1989) and in the formation of the conduction system of the heart (Kirby & Stewart, 1983) and the trigeminal ganglia (Moody & Heaton, 1983). It has become apparent in recent years, since the important paper of Bolande (1974), that there is a whole group of otherwise heterogeneous associations among disease conditions, both in adults and infants, which are best seen as anomalies of development of the NC, the so-called "neurocristopathies." Bolande (1981) has called Von Recklinghausen's neurofibromatosis "the quintessential neurocristopathy," (and one which is certainly under genetic control, see Wallace, Marchuk, Andersen, Letcher, Odeh, Saulino, Fountain, Brereton, Collins *et al.*, 1990); indeed, NC development as a whole is almost certainly influenced strongly by homeobox genes (Hogan, Holland, & Lumsden, 1988; Holland, 1988; Robert, Sassoon, Jacq, Gehring, & Buckingham (1989). Other conditions included among the neurocristopathies, as listed by Hall and Hoerstadius (1988), include phaeochromocytoma, neuroblastoma, medullary carcinoma of the thyroid, carcinoid tumors, chemodectoma of the middle ear, Hirschsprung's disease, neuroectodermal pigmented tumor, clear cell sarcoma, Sipple's syndrome, multiple mucosal neuroma syndrome, Wermer–Zollinger–Ellison syndrome, neurocutaneous melanosis, mandibulofacial dysostosis, otocephaly, CHARGE association (Coloboma, Heart disease, Atresia of choanae, Retardation of physical and mental development, Genital hypoplasia in male and Ear anomalies and/or deafness), albinism, Waardenburg syndrome, and Di George Syndrome. Additionally, Bolande (1974) includes the rare melanotic progonoma, and more recent candidates as neurocristopathies include cystic hygroma of the neck (Miyabara, Sugihara, Maehara, Shoun, Tasaki, Yoshida, Saito, Kayama, Ibara, & Suzumori, 1989) and Fallot's tetralogy in association with glaucoma (Radford & Thong, 1989).

In passing, it should also be noted that a wide range of teratogens seem to act by modifying NC development, in particular Vitamin A (retinoids) (Thorogood, Smith, Nicol, McGinty, & Garrod, 1982), isotretinoin (Smith-Thomas, Lott, & Bonner-Fraser, 1987), cadmium (Tassinari & Long, 1991), dioxins (Pratt, 1987), and possibly thalidomide (Stephens & Strecker, 1983) and that these can frequently result in asymmetric defects as in hemifacial microsomia in the rat and mouse (Hall & Hoerstadius, 1988).

From such vast lists of the cells, tissues, organs, and diseases involved in the NC, it is clear that testing the GBG hyposthesis would be very difficult if, in principle, each of these tissues or organs could be associated with AD or learning difficulties. Before, however, attempting to review the very limited literature on that question, we must also reassess the evidence that GBG used for arguing *for* such an association in the first place.

The core of the GBG hypothesis is that fetal testosterone levels can modify a range of developmental events, including the production of AD and learning disorders, and the development of the NC (see Fig. 1). In postulating a link between NC disorders and AD and learning disorders, the theoretical model of GBG is therefore entirely contingent upon *testosterone modifying the development of the NC*. If that postulate fails then all else in the model is vulnerable, and therefore we must first look at the evidence provided by GBG for such a link, and we must then look to see whether additional evidence is present in the literature.

GBG provide only a very limited amount of evidence in favor of testosterone affecting NC development (approximately 23 lines of text, with not a single cited reference—Geschwind & Galaburda, 1987, pp. 157–158). They begin by stating that "*indirect* evidence exists that sex hormones play a role in crest development, although this has to our knowledge not yet been studied directly" (p. 157). (The essence of the evidence is that melanoma cells sometimes have estradiol receptors, as also can intracranial meningiomata, and GBG note an association between meningiomata and breast cancer.) They also note that neurofibromatosis typically worsens at puberty, particularly in females, and in pregnancy.

As cited, this evidence is weak. To take one example, a recent volume on neurofibromatosis (NF) (Riccardi & Mulvihill, 1981) has only two references to sex differences or sexual development, stating that in fact both precocious puberty and delayed sexual development can occur in NF (Rubenstein, Mytilineoau, Yahr, & Revoltella, 1981) and that in general neurofibromatosis has "no sex predilection," except in the case of neural malignancy in which there can be an excess of female cases (Hope & Mulvihill, 1981). Neither study seems to provide even moderately strong indirect evidence for a pivotal role of testosterone in NC development.

Direct evidence is conspicuously lacking. None of the major works on the NC (Hall & Hoerstadius, 1988; Le Douarin, 1982; Maderson, 1987) mentions any evidence that testosterone affects crest development. A search through the Life Sciences Collection on CD-ROM for the period Jan, 1982–June, 1991, found 307 references which included the term NC and 4919 which included the terms "testosterone" or "androgens" or "sex hormones." No paper mentioned both terms in its title, keywords, or abstract. In passing, it is perhaps worth noting that other hormones, such as glucocorticoids (Smith & Fauquet, 1984) and hydrocortisone (Ferguson, unpublished results—see p. 78 of Le Douarin, 1982), do seem to modify NC migration, although this is hardly relevant as such to the specific hypothesis of GBG. In short, there appears to be little theoretical basis for accepting GBG's central postulate of an association between testosterone levels and NC development.

Asymmetries in neural crest development. GBG speculate, on the basis that there exists a predominance of lateral ventricle meningiomata on the

left side, that NC migration may be inherently asymmetric (although this would seem to have no direct implication for an effect of testosterone). Certainly the role of the NC in the formation of the trigeminal ganglia (Moody & Heaton, 1983), in limb morphogenesis (Shoobridge, Velkou, & McCredie, 1983), in facial devleopment, and in palatal development and fusion (Been, Song, & Van Limborgh, 1984) could be compatible with known asymmetries in the pathologies associated with these organs, such as in trigeminal neuralgia (Rothman & Wepsic, 1974), in limb aplasia (Dlugosz, Byers, Msall, Marshall, Lesswing & Cooke, 1988), in facial asymmetry and hemihypertrophy (Schnall & Smith, 1974), and in cleft lip and palate (Sanders, 1933). Nevertheless, it must be remembered that even if these speculations are correct, they cannot provide substantive evidence in favor of the GBG theory, since they do not invoke testosterone, and do not make predictions about associations with learning deficits or AD. Nevertheless, such asymmetries might include such obscure cases as that in which a mentally retarded individual showed both facial and bodily asymmetry, along with hyperpigmented areas restricted to only one side of the body (Chemke, Rappaport, & Etrog, 1983); since culture of fibroblasts from the affected side showed trisomy-18, whereas those from the other side were normal, the implication is that the defects resulted from an impaired, asymmetric NC migration, presumably resulting from a lateralized trisomy-18 mosaicism.

Having given this brief introduction to the NC, let us now examine the data relating AD to NC disorders.

CLEFT LIP/PALATE. Fraser and Rex (1985) did not detect an association between side of cleft and handedness in children with cleft lip or palate, although they simply lumped left-handers, "switched" left-handers, and ambidexters into a single group. They did, however, note that the parents of children with right clefts were more likely to be non-right-handed than other parents. They also cite Rintala (1985) as showing that patients with left-sided or bilateral clefts are more likely to be left-handed. Such data do not provide any convincing evidence for an association between AD and cleft lip/palate.

PIGMENTATION. Schachter et al. (1987) obtained data on learning disabilities, hair color, and handedness from a sample of 1117 randomly selected professionals. They found that 16% of blondes, but only 12% of nonblondes had handedness scores less than 0 (left-handed) and that 28% of blondes but only 12% of nonblondes scored in the 0–70 range. If the split is made at +70, the difference is highly significant ($p < .001$). However, the major reason for this is the excess of weak right-handers. If the sample is divided at LQ = 0 into left-handers and right-handers, the subsequent χ^2 (1.75) is not significant. Urion (1988) reported that a subgroup of dyslexic boys all had fathers who had become prematurely grey, but reports no data on greying in the parents of his other dyslexics or his

control sample. Bryden and McManus (1992a), in a survey of undergraduate students, were unable to find any significant association between handedness and either eye color or hair color. Similarly, Steenhuis, Bryden, and Schroeder (1993) found no association between handedness and premature greying in a large sample of young adults. At present, then, there is no strong evidence to suggest a relation between handedness and either premature greying or natural hair or eye color.

DOWN SYNDROME (TRISOMY-21). Individuals with Down syndrome (trisomy-21) have frequently been identified as having some degree of anomalous cerebral lateralization. There is, for example, general agreement that Down syndrome individuals manifest an elevated incidence of non-right-handedness (Batheja & McManus, 1985; Elliott, 1985; Pickersgill & Pank, 1970; Pipe, 1987). However, this effect seems to be due to the fact that such people lack a consistent hand preference, rather than that they have an elevated incidence of left-handedness (Bishop, 1990a; Soper, Satz, Orsini, VanGorp, & Green, 1987).

A number of studies (reviewed by Elliott, Weeks, & Elliott, 1987) have shown that Down syndrome individuals show either no ear advantage (Sommers & Starkey, 1977) or a left-ear advantage (Hartley, 1981; Pipe, 1983; Zekulin-Hartley, 1981, 1982) on verbal dichotic listening tasks. Such performance is normally taken as evidence for right-hemispheric specialization for speech perception rather than the more common left-hemispheric specialization. As Elliott et al. (1987) indicate, Down syndrome persons also tend to show superior performance when compared to mental-age-matched controls on tasks involving visual pattern discrimination or visuomotor performance. Thus, Down syndrome people are better at simultaneous processing tasks and worse at sequential tasks. Elliott et al. (1987) suggest that Down syndrome individuals use the right hemisphere for processing speech input, but, like others, use the left hemisphere for the control of speech and for other complex sequential motor tasks. They see this dissociation of speech perception from langauge output as underlying some of the language problems manifested by those with Down syndrome.

While these data may indicate some anomalies of cerebral lateralization in Down syndrome children, the effects, like those of autism, may be just as easily explained by the view that ambiguous handedness and poor language lateralization are characteristic of the mentally handicapped.

CANCERS. Breast cancer is more common in the left breast than the right (see McManus, 1977, for a review). Howard, Petrakis, Bross, and Whittemore (1982) found no relation between handedness and side of breast cancer. However, Howard et al. cite Senie, Rosen, Lesser, Snyder, Schottenfeld, and Duthie (1980) as finding an excess of left breast cancer in left-handed women, although the association just failed to reach statistical significance. King, Lynch, and Selvin (1979) found no evidence

for concordance of side of breast cancer with handedness, in agreement with Anderson, Goodman, and Reed (1958), but in contrast to Penrose, Mackenzie, and Karn (1948) and Busk (1948). King et al. (1979) postulate that the laterality of breast cancer is determined by environmental factors and cite the women of the Tanka or "boat" population in Hong Kong, who nurse from one breast only. Among 34 such women who developed cancer, 27 (79%) had tumors in the unused breast.

Kramer, Albrecht, and Miller (1985) suggest that left-handed women are more likely to develop breast cancer before the age of 45, but that the overall incidence is not higher in left-handers. Recently, however, Olsson and Ingvar (1991) reported that there was a significantly lower incidence of breast cancer among left-handed Swedish women than among those who were right handed.

Ignoring the lateralization of the cancer, Sandson, Wen, and LeMay (1992) found that right-handed white women with breast cancer were less likely than controls to show a larger right frontal width or left occipital width on CT scan. In their patient population without metastases, 49% showed reversed frontal lobe asymmetry, with the left side being wider than the right, and 49% also showed reversed occipital asymmetry, with the right being wider than the left. The side of the cancer was, however, unrelated to the anatomical asymmetry. The authors suggest that intrauterine exposure to gonadal hormones, such as testosterone, may serve both to alter brain development and to predispose the individual to cancer later in life. McManus (1992) has argued that these data are interpretable in terms of fluctuating or random asymmetry rather than reversed asymmetry.

Swerdlow, Huttley, and Smith (1987) reported a lower incidence of left-handedness or ambidexterity in testicular cancer patients (11%) than in controls (16%). In addition, they reported a lower incidence of left-handedness (9%) in those with noncancerous cryptorchidism and/or hernia.

From this evidence, we can conclude that there is little data to support the view that there is a concordance between handedness and the side of breast cancers. Furthermore, while breast cancers in general do not seem to be related to handedness, testicular cancers may actually be less common in left-handers.

OTHER PHENOMENA. The GBG model suggests that cerebral arteriovenous malformations (AVMs) would be more common in the left hemisphere of male patients. Barr, Jaffe, Wasserstein, Michelson, and Stein (1989) examined AVMs in 112 cases and found that women were more likely than men to have left-hemisphere AVMs and that this effect was not modulated by handedness. Non-right-handers, however, did tend to have more frontal AVMs, regardless of side. The authors see these data as inconsistent with the GBG model.

Neural Crest and Language Disorders

Behan et al. (1985) indicate that dyslexics have a high incidence of blue eyes and fair hair. Schachter et al. (1987), investigating a large sample of professionals, reported a borderline tendency for blondes to be more likely to report learning disabilities. They indicate that subjects with learning disabilities were almost twice as likely to be blonde as non-learning-disabled subjects. Urion (1988) claims that those dyslexics whose families have a history of immune disorders also have a high frequency of premature greying.

Christenson and Sacco (1989) surveyed 199 stutterers about handedness, original hair color, gender, and age. They reported both that stutterers were more non-right-handed than nonstutterers and that disfluency was greater among those with blonde hair and blue eyes, and among females. They argued that stuttering, therefore, may be related to the influence of testosterone and hypopigmentation factors.

Probably the most fascinating evidence comes from a study by Dlugosz et al. (1988). They studied 80 children with congenital upper limb reduction deficits. They were categorized as to whether they had learning difficulties in school, as evidenced by placement in a learning disability class or by failure. Among the boys with right-sided defects, 54% had learning difficulties and 70% had reading problems, while the comparable figures for left-sided defect were 14% in both instances. Among girls with right-sided defects, the figures were 24 and 24%, while among those with left-sided defect, they were 10 and 16%. One should probably obtain a control group of early childhood amputees, but these data are highly suggestive of a link between the development of the upper limb and language function.

Neural Crest Disorders and Immune Deficits

The GBG theory clearly makes the prediction that individuals with putative NC disorders (such as blue eyes, blonde hair, or premature greying), as well as the broader range of neurocristopathies, should show immune deficits. For instance, Scheuerle, Good, and Habal (1990) have reported a high incidence of immune disorders in a small sample of individuals with cleft lip/palate.

It must, however, be noted that although such associations are indeed a prediction from the GBG theory, they can hardly be considered as evidence in favor of it. The thymus gland is itself determined in part by NC tissue (Hall & Hoerstadius, 1988) and hence, an association of NC disorders and immune deficits need not invoke testosterone as a causal mechanism. This is seen most clearly in the rare neurocristopathy known as Di George's syndrome, which is a pure deficit of T-cell development and presents immunologically with abnormal immunoglobulins of the IgG and IgA types; the thymus is histologically normal but is usually smaller

than normal and in an ectopic site. The presence of other defects (such as of the heart, ears, and facies) suggests that the syndrome is, in part at least, the result of NC maldevelopment (Hall & Hoerstadius, 1988), a hypothesis that seems to be supported by direct empirical evidence (Bockman & Kirby, 1984). Interestingly, individuals with Fallot's tetralogy also seem to show abnormalities of facial appearance as well as immune deficit (Radford & Thong, 1989), showing how NC abnormality can produce a cluster of apparently unrelated features which otherwise might be interpreted in terms of the GBG hypothesis.

Di George's syndrome shows the difficulties of testing a theory as complex as that of GBG in the general absence of direct measures of intervening variables such as testosterone and in the presence of competing embryological explanations which, although more restricted in scope, are supported by more direct experimental evidence.

Minor Associations

Relations between Anomalous Dominance and Language Disorders

Lateralization and dyslexia. It is part of the lore of the learning disability literature that children who are developmentally dyslexic are frequently left-handed. The hard evidence on this point is more ambiguous. For example, Satz and Fletcher (1987) present data relating handedness to reading ability in Satz's large study of children in Florida and conclude that there is no association between handedness and reading ability. They argue that the positive evidence comes from small samples in which the selection of the control group may be suspect, while large epidemiological studies, in which a very large random sample of the population is assessed, fail to find evidence for a relation between the two variables. Similar findings have been reported by Belmont and Birch (1965) and by Bishop (1984). In contrast, Annett (1985), in her review of the language disorder literature, concludes that there is good evidence for an elevated incidence of left-handedness in poor readers.

Bishop (1990a), in her review of handedness and developmental disorder, criticizes studies like those of Satz and Fletcher (1987) on the grounds that they are primarily concerned with poor reading, rather than with specific reading disability. She argues that the term developmental dyslexia should be confined to those who are not only poor readers but are also performing at a normal intellectual level in other areas. Bishop (1990a, pp. 124–125) summarizes the data from 25 studies that meet these criteria and concludes that the evidence for an association between handedness and reading disorder is weak and inconsistent. However, she notes that her data are very heavily influenced by the very large British National Child Development Study (Bishop, 1984), wherein no difference between those with specific reading retardation and others in the inci-

dence of left-handedness was found. Of the remaining 24 studies in her survey, 17 report a higher incidence of left-handedness in the retarded readers, and the overall rate of left-handedness in these studies is 11.2% in the dyslexics as opposed to 5.8% in the control subjects.

More recently, Hugdahl et al. (1990) found no elevation of left-handedness in a study of 105 dyslexic children and their controls. However, Obrzut and Atkinson (1993) report a higher incidence of left-handedness in 33 learning-disabled children than in 88 normal readers. In a much smaller study, Hynd et al. (1990) noted that 3 of their 10 dyslexics but none of 10 attention deficit disorder/hyperactivity children and none of their 10 controls were left-handed. With such a small sample, however, it is impossible to draw firm conclusions. In summarizing 4 large-scale family studies of reading disability, Gilger et al. (1992) found signs of an elevated incidence of left-handedness in the relatives of reading-disabled subjects in only one study. Curiously, in that study handedness was assessed by asking the respondents whether they wrote and used a fork with the right or left hand or both, and the incidence of left-handedness was significantly elevated in both the reading-disabled relatives of the subjects and in their relatives who were not reading-disabled. In the other studies the Edinburgh Inventory was employed and subjects were primarily classified as strong right-handers or non-right-handers, thus leading to a much higher estimate of non-right-handedness. In two of the latter studies, the mean Edinburgh score was actually higher in the reading-disabled relatives than in the non-reading-disabled relatives. Gilger et al. (1992) conclude that handedness does not vary systematically as a function of reading disability.

Schachter et al. (1987) studied learning disabilities, hair color, and handedness in 1117 randomly selected professionals. They found that 8% of the left-handers and 16% of those with LQs between 0 and +70 reported learning disabilities, while only 3% of the strongly right-handed did. This is highly significant when the split is at +70, and remains significant when the split is at 0.

Given all these conflicting data, it is difficult to come to a firm conclusion. However, the Bishop (1990a) survey does suggest that the incidence of left-handedness is nearly twice as high in dyslexics as in normal controls, when dyslexia is considered to be reflected in poor reading but otherwise normal intellectual functioning. While the studies subsequent to the Bishop (1990a) survey are also inconsistent, they tend to reflect a similar pattern.

In many ways, the more telling evidence concerns other measures of cerebral lateralization. In a review of the literature on dichotic listening performance and reading disability, Bryden (1988a) concluded that the majority of such studies indicated that right-handed poor readers were less likely to show the right-ear advantage for dichotically presented ver-

bal material that is characteristic of normal right-handed readers. More recently, Obrzut, Boliek, and Bryden (1990) have reported that poor readers perform abnormally on nonverbal tests of right-hemisphere function.

Furthermore, numerous studies (e.g., Galaburda & Kemper, 1979; Galaburda et al., 1985; Hier, LeMay, Rosenberger, & Perlo, 1978; Hynd et al., 1990) have shown that there is a high incidence of abnormal anatomical asymmetries in dyslexics. Galaburda et al. indicate that the temporal plana of dyslexics are of equal size rather than being larger on the left, as is normally the case. Such a finding would be consistent with the notion that the underlying lateralizing mechanism has been disturbed, leaving anatomical asymmetries to chance fluctuation.

Lateralization and developmental language disorders. Many children who ultimately have difficulty in learning to read show early developmental language disorders, either in the form of impairments in phonology or in severe grammatical difficulties (Tallal & Katz, 1989). Assessment of the relation between developmental language disorders and handedness is made complex by the fact that such disorders are often detected in quite young children, and the techniques for measuring handedness are often crude or idiosyncratic. While some early reports (e.g., McAllister, 1937) suggested that the incidence of left-handedness in children with phonological disorders was quite high, subsequent research has provided only modest support for such a view. Thus, Neils and Aram (1986) and Bishop (1990b) found no significant handedness differences between language-impaired children and normal controls, while Ingram (1959) reported no difference between groups in the incidence of left-handedness, but a much higher percentage of poorly lateralized children in the language-impaired group. However, Morley (1972) found that some 26% of a sample of 96 children with articulatory difficulties were left-handed, and another 14% were poorly lateralized. An increased incidence of left-handedness, therefore, may be specific to children showing early articulatory problems, rather than being characteristic of all developmental language problems (see Bishop 1990a).

Lateralization and autism. With other language disorders, the situation is more clear. Thus, for instance, it seems true that the incidence of left-handedness is elevated in autism. The relationship between handedness and autism has been summarized by McCann (1981), by Fein, Humes, Kaplan, Lucci, and Waterhouse (1984), and by Bishop (1990a). The general pattern that emerges is that autistic children show an increased incidence of left-handedness (18%, according to Fein et al.), and, at the same time, show a reduced degree of handedness such that 36% (according to Fein et al.) fail to show a preference for either hand. Satz, Soper, Orsini, Henry, and Zvi (1985b) and Soper, Satz, Orsini, Henry, Zvi, and Schulman (1986) have made use of autistic children in developing

their concept of "ambiguous handedness." They retested autistic subjects on a handedness battery, noting that many subjects were inconsistent in their hand useage for an activity across repeated testings and argued that these subjects really had not developed any hand preference. Overall, their data indicate 44% right-handed, 22% left-handed, and 36% without preference. McManus, Murray, Doyle, and Baron-Cohen (1992) have found that autistic children often indicate preference for the use of one hand, but fail to show skill differences favoring the preferred hand. On the basis of these data, they suggest that hand preference precedes differences in hand skill.

In general, the data on handedness and autism indicate that the incidence of both left-handedness and the lack of hand preference is elevated. While this might be taken as support for the GBG position, it is perhaps better explained by the concept of ambiguous handedness (Satz et al., 1985b; Soper et al., 1986). Satz and his colleagues have argued that many autistic children simply have failed to establish a clear hand preference and thus are less strongly right-handed than normal children. Furthermore, there is some evidence (Bishop, 1990a; Bradshaw-McAnulty, Hicks, & Kinsbourne, 1984; Hicks & Barton, 1975; Lucas, Rosenstein, & Bigler, 1989) that the incidence of ambiguous or ill-defined hand preference is elevated in the mentally handicapped. The increased incidence of left-handedness in autism, then, may not be a consequence of the language disturbance, as implied by the GBG model, but a reflection of the severe mental impairment.

Prior and Bradshaw (1979) tested autistic children on a dichotic listening task and found that they did not show a clear right-ear advantage. In addition, Dawson, Finley, Phillips, and Galpert (1986) found that autistic children did not show the asymmetry of evoked response to auditory speech stimuli characteristic of normal children.

Thus, the data on autistic children seem to show fairly clearly that autism is associated with both anomalous handedness and disturbed lateralization of speech functions. However, as with developmental dyslexia and dysarthria (articulatory disorders), there appears to be a major increase in the incidence of poor lateralization, and therefore autism may be associated with a failure of the normal lateralizing mechanism rather than with a specific increase in left-handedness.

Lateralization and stuttering. With respect to stuttering, the majority of studies seem to find some evidence for either an increased incidence of left-handedness or a reduced degree of right-handedness in this population (Christensen & Sacco, 1989; Records, Heimbuch, & Kidd, 1977; Rosenfield, 1980; Vaughn & Webster, 1989). Calnan and Richardson (1976), however, reported that non-right-handedness was associated with teacher-assessed poor speech, but not with medically assessed stuttering.

Marchant-Haycox et al. (1991) did not find an association of handedness with stuttering, and Fitzgerald, Cooke, and Grenier (1984) seem to imply that stutterers are *more strongly* handed; they report that stutterers are particularly bad in handwriting with the nondominant hand. Strub, Black, and Naeser (1987) find increased evidence of AD in the siblings of stutterers. Furthermore, Gotestam (1990) found an increased frequency of both left-handedness and stuttering in architects, although it is not clear that the two are specifically related. Despite the above data, Bishop (1990a), in her review, concludes that the bulk of recent studies have found little or no evidence for an increase of non-right-handedness in stutterers.

Some studies report reduced right-ear effects for verbal dichotic tasks in stutterers (Curry & Gregory, 1969; Sommers, Brady, & Moore, 1975), although two smaller studies failed to replicate this finding (Brady & Berson, 1975; Slorach & Noehr, 1973), and Sussman and MacNeilage (1975) found a lack of right-ear effect only for pursuit auditory tracking.

In general, then, there is at least reasonable evidence for associations between both handedness and reduced left-hemispheric speech lateralization in stutterers compared to nonstutterers.

Lateralization and Tourette syndrome. TS, as mentioned earlier in connection with immune system and specific language–disability relations, is associated with an elevated frequency of dyslexia and stuttering and, as such, might be considered to be a disorder involving language mechanisms. Although Shapiro, Shapiro, and Wayne (1972) found a very high incidence of left-handedness (35%) in TS patients, a much larger study by Comings and Comings (1987) failed to confirm this. If we use the Comings and Comings data on writing hand and combine the data from the two studies, the incidence of left-handedness in 295 TS patients is 14.6%, while Comings and Comings report a figure of 14.5% for their 47 control subjects.

To summarize, in general there is at least modest evidence for an association between handedness and some developmental disorders of language. Thus, left-handedness or ambiguous handedness appears to be more common in dyslexia, in autism, in articulatory disorders, and in stutterers and the normal anatomical asymmetries of the brain appear to be less common in developmental dyslexics, but there appears to be no elevation of non-right-handedness in Tourette syndrome. To a large extent, the data reflect an increased incidence of poorly lateralized individuals, rather than an increase in the proportion of left-handedness. Such data may indicate a breakdown of the normal lateralizing mechanisms rather than a true increase in left-handedness. Thus, while these data may be viewed as being at least moderately consistent with the GBG hypothesis, they can almost certainly be accommodated by other models (e.g., Bishop, 1990a; Satz et al., 1985b) just as readily.

Anomalous Dominance and Giftedness

The GBG model predicts that abnormal left hemisphere development will be followed by a compensatory overdevelopment of the right hemisphere, thus leading to enhanced right-hemisphere function. Thus, it predicts that AD should be associated with exceptional talent in music, art, and spatial ability. While one should expect such an effect to be most clearly manifest in true genius, the enhancement of right hemisphere performance in those with AD would also lead one to expect at least some association between handedness and intellectual ability in normal populations. The evidence concerning exceptionally talented individuals (including university professors and students) will be presented first, followed by results from studies involving measures of spatial and verbal ability in normal individuals.

Gifted individuals and those with above average intelligence. Hicks and Dusek (1980) found an increased incidence of weak- or mixed-handedness in children with high IQ, although they interpreted this as an increase in non-right-handedness. Similarly, Lewandowski and Kohlbrenner (1985) found a decrease in right-sidedness in gifted children, although their data do not indicate whether this is due to differences in handedness, eyedness, or footedness. Benbow (1986) has reported an elevated incidence of left-handedness in precociously verbal or mathematical children. Thus, there are indications that the very gifted, whether their abilities lie in mathematics or in verbal skills, are more likely to be left-handed or ambidextrous.

The evidence concerning specifically elevated right-hemisphere function, as might be expected from the GBG model (1987), is equivocal. Rosenblatt and Winner (1988) found a very high incidence of left-handedness and ambidextrality in a small sample of children with exceptional drawing ability. Likewise, Hassler and Gupta (1993) found higher scores on a musical talent measure in left-handers, as well as a reduced dichotic right-ear advantage in the musically talented. There are also indications that the incidence of left-handedness is elevated in hyperlexic children (Aram & Healey, 1988; Healey, Aram, Horwitz, & Kessler, 1982), a finding that is interesting in the light of claims that dyslexics are more likely to be left-handed (e.g., Annett, 1985) and considering that reading is principally a function of the left hemisphere. In adults, Cranberg and Albert (1988) report an elevated incidence of non-right-handedness in high-level male chess players, but signs of a reduction in the incidence of left-handedness in female chess players of similar quality. On the other hand, Temple (1990) did not find any clear relationship between handedness and discipline among Oxford University faculty, the only significant difference emerging after a post hoc subdivision of the subjects.

Newland (1981) reported that left-handers scored higher than right-handers on a test of creative thinking. Kimura and D'Amico (1989) have reported that nonscience university students who are not strongly right-handed are less lateralized than are right-handers on a dichotic listening task and are also poor in spatial abilities; in contrast, non-right-handed science students show the right-ear effect seen in right-handers and are high in spatial ability. Smith, Meyers, and Kline (1989) reported that left-handers showed a higher incidence of self-reported mathematical and artistic talents than right-handers and a lower incidence of self-reported verbal skills. In their study, the incidence of left-handedness was related to stuttering, asthma, eczema, and epilepsy in the subjects' parents. Little evidence for an association between handedness and musical ability was found by Byrne (1974), although there were somewhat more mixed-handers among instrumental music students (in contrast to Oldfield, 1969). Casey and Nuttall (1990) reported that college women with AD—defined as either non-right-handedness or as having a non-right-handed first-order relative—were more likely to be masculine (M + F −) on the Bem Sex Role Inventory and scored lower on the feminine activities and love/marriage subscales of a test of tomboyism. Again, one should note that the definition of AD has been expanded to include familial sinistrality as a defining attribute.

At best, these data indicate modest evidence for an increased incidence of left-handedness or ambiguous handedness in those people who are either intellectually very gifted or who have specific artistic or musical talents well above average.

Normal people: general cognitive ability. Since a large portion of the normal population manifest AD in one sense or another, the GBG model also implies that there should be a relation between handedness (or AD) and both verbal and spatial skills. Left-handers should be better than average at spatial tasks and worse than average at verbal ones. Large-scale population surveys have not borne this out. For example, Porac and Coren (1981; Table 10-2, pp. 162–163) summarized 29 studies in which normal subjects, ranging from 4 years of age to adult, were tested on various measures of cognitive ability. They found that only 18 of the 29 studies reported any association between handedness and verbal, spatial, or "general" cognitive ability. Most of the negative findings were found in the studies with children, and reports of associations were not consistent. Of the 10 adult studies reporting a significant relationship, 9 report that right-handers are better on at least one of the three categories of ability, and 2 report that left-handers are better, 1 showing that left-handers are better in spatial ability and 1 that they are better in verbal ability.

Normal people: spatial ability. On various measures of spatial ability, no differences between left-handers and right-handers were found by

Fennell, Satz, Van den Abell, Bowers, and Thomas (1978), Newcombe and Ratcliff (1973), Newcombe, Ratcliff, Carrivick, Hiorns, Harrison, and Gibson (1975), Heim and Watts (1976), or Gibson (1973). Heim and Watts (1976) did find some suggestion that left-handed males did better than right-handed males on tests of numerical ability. Furthermore, the data of Newcombe et al. (1975) provide some suggestion that left-handed men are worse than right-handed men in Performance IQ, while the reverse is true for women. However, a subsequent analysis of the Newcombe et al. (1975) data (Mascie-Taylor, Gibson, Hiorns, & Harrison, 1985) failed to reveal a significant contribution of handedness to any of the spatial subtests. Contrary to the GBG prediction, Nebes (1971) reported that left-handers were poorer at perceiving part–whole relations, and Silverman, Adevai, and McGough (1966) claimed that left-handers were poorer on a variety of perceptual tasks.

In studies with younger subjects, Hardyck, Petrinovitch, and Goldman (1976) found no relation between handedness and nonverbal IQ and spatial ability tests in a large sample of school children. Sheehan and Smith (1986) found no relation between spatial ability and either handedness or visual laterality in boys aged 11–13 years.

Sanders, Wilson, and Vandenberg (1982) reported a relation between handedness, sex, and spatial ability in the Hawaii Family study. In general, left-handed men were superior to right-handed men, but left-handed women were worse than right-handed women. A similar finding, on a much smaller sample, was reported by McGee (1976). Later, McGee (1978) reported an association between weaker right-handedness and higher mental rotation scores in groups of men and women and their parents. In high school students, Yen (1975) found that left-handed males were poorer than right-handed males, but that there was no difference in females. These studies would suggest that the relation between handedness and spatial ability depends on sex.

Other studies have found that it is those with weak hand preferences who are deviant. Thus, Miller (1971) found that mixed-handed undergraduates, using Annett's (1967) classification, were inferior to right-handers on a spatial test, but not on a verbal one. In sharp contrast, Burnett, Lane, and Dratt (1982), using a test of spatial visualization, found that the poorest performance occurred in subjects who were either extremely LH or extremely RH.

This brief review makes it clear that there are complex interactions among sex, handedness, and spatial ability, and this is not the place to advance a theoretical interpretation. It is clear, however, that the vast majority of studies fail to find the positive relation between spatial ability and AD predicted by the GBG theory.

Normal people: verbal ability. Again, there is little indication in the literature that left-handers or those with AD are inferior to right-handers

in general verbal ability. Hardyck et al. (1976) found no relation between handedness and various IQ and verbal ability tests in a large sample of school children. Likewise, Longoni, Scalisi, and Grilli (1989) found no relation between lateral preference and verbal skills in Italian elementary school children. Sheehan and Smith (1986) found no relation between handedness or visual measures of lateralization and verbal ability.

With an adult sample, no effects of handedness were reported by Heim and Watts (1976). It is true that Newcombe et al. (1975), in a large-scale study of Oxfordshire villagers, found that those who performed at least one of seven activities with either hand had higher verbal IQs (VIQ) than other subjects. While a reclassification of their subjects suggests that somewhat higher VIQs are found in left-handed women, and in left-handed or mixed-handed men, a subsequent analysis of the same data (Mascie-Taylor et al., 1985) failed to reveal a significant contribution of handedness to any of the verbal subtests.

In summary then, while there are some hints that there may be an elevated incidence of left-handedness in those who are extremely talented, the data are generally quite consistent in failing to shown any relation between handedness or AD and general verbal or spatial ability within the normal range.

Testosterone Effects

In the GBG model, it is the level of fetal testosterone that is hypothesized to alter immune function, handedness, and language development. While studies on testosterone levels in adults are becoming increasingly common, we know little about fetal testosterone effects on behavior.

Tan (1990a,b,c, 1991a,b,c) has investigated the relation between serum testosterone levels and hand performance extensively. In a 1990 (1990c) study, he reported that serum testosterone levels correlated with right-hand skill on a modified version of the Annett pegboard: right-handed men showed a positive correlation between serum testosterone level and right-hand skill, while right-handed women showed a negative correlation. This would suggest that high testosterone levels are associated with increased right-hand skill in men, but with decreased right-hand skill in women. In a further study, Tan (1990b) found that right-hand superiority on the Tapley and Bryden (1985) dot-filling task increased with increasing serum testosterone level in males, but was unaffected by testosterone in women. Next, Tan (1991a) showed that high testosterone levels in right-handed women were associated with poorer peg-moving performance and less improvement with practice, generally replicating his 1990 (1990a) study. Subsequently, Tan (1991b) found the reverse pattern in male subjects. These findings generally show that increased serum testosterone is associated with increased right-handed performance in men, but

not in women. However, Tan (1991c) has also reported that testosterone levels are significantly higher in both men and women with AD than in those with standard dominance, when the AD group includes left-handers, weak right-handers, and right-handers with a history of familial sinistrality. This latter finding is in general agreement with Tan's (1990a) report that degree of hand preference is negatively correlated with testosterone level in right-handed women and in right-handed men without a history a familial sinistrality, but not in right-handed men with a familial history of sinistrality. However, Tan's studies of hand skill (1990b,c, 1991a,b) suggest that increased levels of testosterone are associated with stronger right-handedness, at least in men. Given the relatively small sample sizes employed in these studies (usually about 45 men and 20 women), the large number of potential confounding factors (eye dominance, footedness, and intellectual ability, to name a few), and the apparent inconsistencies in the effects on preference and on skill, it is unclear how best to interpret these data.

Wexler, Mason, and Giller (1989), studying psychiatric patients with affective disorder, found that testosterone levels were significantly lower in those patients with relatively large dichotic right-ear advantages. This would imply that those with high testosterone levels were relatively weaker in their left hemisphere lateralization for language, in accordance with the Geschwind hypothesis.

Hassler (1991) has reported decreased levels of salivary testosterone in male musical composers and increased levels of testosterone in female musical composers, suggesting a minimization of sex differences in creative musicians. Similar effects were not found with musical performers or artistic painters.

Christiansen and Knussman (1987) have also reported relations between testosterone and cognitive ability in men, with testosterone levels correlating positively with spatial relations and negatively with sequential tasks. However, Moffat and Hampson (1993) have found that salivary testosterone levels are significantly lower in left-handers than in right-handers. While circulating testosterone levels in adults may not correlate well with fetal exposure to testosterone, these data provide suggestive evidence against the Geschwind hypothesis—one would expect higher, rather than lower, levels of testosterone in left-handers.

Most critical for the Geschwind hypothesis, however, are the data such as those of Grimshaw, Niccols, and Finegan (1990). They studied the handedness and dichotic listening performance of 7-year-old children whose mothers had undergone amniocentesis and from whom fetal levels of testosterone could be assessed. They found that increased levels of fetal testosterone resulted in no differences in handedness, although increased right-ear effects were found on a verbal dichotic listening task. In a follow-up study, using more reliable measures of laterality, Grimshaw,

Bryden, and Finegan (1993) found that increased prenatal testosterone levels were associated with stronger right-handedness and stronger right-ear effects on the dichotic listening test in girls. Both these findings are contrary to the predictions of the GBG model.

Furthermore, 1 of the 13 (7.7%) androgen-insensitive cases studied by Imperato-McGinley, Gautier, Pichardo, Voyer, and Bryden (1991) was left-handed. Since androgen-insensitives do not have the receptors for testosterone, they should not be left-handed, according to the GBG model. At the very least, the Imperato-McGinley et al. (1991) case indicates that there must be some route to left-handedness other than the one postulated by Geschwind and Galaburda (1987).

CONCLUSIONS

What are we to conclude from this review of what seem diffuse and often seemingly interconnected studies, with their ofttimes inconsistent findings? We have assessed the evidence for interrelations among five broad categories of variables: AD, language disorders, giftedness, immune disorders, and NC disorders. The evidence is fairly strong for an association between AD and language disorder, with the incidence of some form of atypical lateralization being more common in developmental dyslexia, autism, and stuttering, although in view of the problems associated with the very concept of AD, it is difficult to know whether it is AD that is the appropriate correlate.

Likewise, there seem to be real associations between handedness and some immune disorders, although some of these associations, such as those with allergies, asthma, and colitis, follow the pattern hypothesized by Geschwind and Galaburda, while others, such as those with myasthenia gravis and arthritis, show the reverse pattern, with right-handers being more at risk. Furthermore, the particular disorders relating to handedness make little sense immunologically, suggesting that it is some other covariate that underlies the relationship. As for most of the other interrelations predicted by the Geschwind and Galaburda (1987) model, there is sparce and ambiguous evidence. Thus, atypical lateralization does not imply giftedness nor NC disorders; language disorders are not related to giftedness, nor to immune disorders (although we feel that the evidence is less clearly negative on this point), nor NC disorders; and giftedness is not related to immune disorders nor to NC disorders.

Finally, the Geschwind and Galaburda (1987) model relates all of these effects to variations in fetal testosterone level. Although testosterone usually acts in the model as a latent and unobservable variable, and hence could be replaced by some "Factor X" (McManus & Bryden, 1991), the few direct studies of variations in testosterone level have not been encouraging. Although there do seem to be associations between adult

TABLE 6
A Summary of the Evidence Concerning the GBG Model

Topic	Rating
Anomalous dominance (AD)	−2
Immune disorders and AD	−1
Immune disorders and giftedness	0
Immune disorders and language disability	+1
Immune disorders and neural crest (NC) disorders	0
AD and language	
Dyslexia	+1
Developmental language disorders	+1
Stuttering	+1
Autism	+1
Tourette syndrome	0
AD and giftedness	
Exceptional talents	−1
Spatial ability	−2
Verbal ability	−2
AD and NC	−1
Language and giftedness	0
Language and NC disorders	0
Giftedness and NC disorders	0
Testosterone effects on AD	−1
Testosterone effects on language	−1
Testosterone effects on giftedness	0

testosterone levels and both handedness and cognitive ability, such studies really beg the question, since it is *fetal* testosterone that is hypothesized as the relevant variable. What little literature there is seems to suggest that fetal testosterone levels do not affect handedness nor cognitive ability in the manner suggested by Geschwind and Galaburda (1987).

In Table 6, we have attempted to summarize the quality of evidence for various aspects of the GBG model. In producing this summary, we have rated each form of evidence on a 5-point scale, using the following criteria.

+2 Several empirical studies by independent groups of researchers provide unequivocal support for hypotheses that are clearly predicted by the GBG model AND are difficult to explain using any other currently available model.

+1 Empirical evidence which is generally consistent with the predictions of the GBG model, BUT which could also be explained by other models.

0 No studies available, OR existing studies seriously methodologically flawed, OR evidence totally ambiguous.

−1 Empirical evidence inconsistent, BUT some good studies inconsistent with GBG model.
−2 Several empirical studies are consistent AND are contradictory to the predictions of the GBG model.

In our opinion, none of the areas of research we have reviewed provides sufficiently compelling evidence for the GBG model to require a rating in our +2 category. There are a few isolated studies stimulated by the GBG model that hint at hitherto unsuspected relations, but they hardly constitute compelling evidence for the model as a whole. In particular, we would cite the reports by Chengappa et al. (1991, 1992) of a relation between the presence of autoimmune antibodies and some aspect of lateralization and the Dlugosz et al. (1988) demonstration of a link between the side of congenitally missing forelimbs and subsequent language disorders. However, until it is determined whether the Chengappa et al. effects are more closely related to handedness or eyedness, their interpretation remains uncertain. Likewise, the Dlugosz et al. study requires a proper control group of children who have adventitiously lost a forelimb prior to the development of language.

Somewhat generously, we have rated several areas in our +1 category, including the relations between AD and many aspects of language development, and that between language disorders and immune dysfunction. However, as Bishop (1990a) has indicated, it is uncertain or ambiguous handedness, not left-handedness per se, that is most clearly elevated in children with developmental language problems, and there are alternative models to account for such effects (e.g., Satz, Orsini, Saslow, & Henry, 1985a).

Furthermore, several studies that have investigated the relation of both immune disorders and handedness to developmental language problems (Burke et al., 1988; Hugdahl et al., 1990; Pennington et al., 1987; Obrzut & Atkinson, 1993) have failed to find the expected three-way relation. Thus, while both left-handedness and immune disorder may be elevated in dyslexics, immune disorders are not more common in left-handed dyslexics than in right-handed ones.

The areas that we have evaluated in the +1 category, then, provide modest support for the GBG model, but other alternatives are at least as plausible. We have rated numerous other categories as "0," largely because the evidence is either lacking or utterly ambiguous, or as "−1," on the grounds that there is at least reasonable evidence that the predictions of the GBG model are not supported.

Several areas provide compellingly negative evidence for the GBG model. One of the more notable is the relation between handedness and immune function, often considered to be the seminal contribution of the model. While our meta-analysis (Tables 4 and 5) indicates that left-handedness *is* more common in people with some immune disorders,

such as allergies, asthma, and ulcerative colitis, it is also *less* common in other diseases, such as arthritis and myasthenia gravis. There is nothing in the original GBG model to indicate that AD would or should provide protection against immune disorder (but see Galaburda, 1990), and the results of our meta-analysis must be taken as strong evidence against the model, although we have rated this area only as "−1" because of the few positive effects. Certainly, the associations we have found seem to require explanation, assuming that they can be further replicated. One possibility is that left-handers and right-handers differ in their HLA antigenic subtypes; Yeo and Gangestad (1993) have reported that left-handers have a higher incidence of the B8, A1/B8, and DR3 haplotypes than do right-handers. Since different autoimmune diseases have different patterns of association with the HLA types (Tiwari & Terasaki, 1986), such a finding might explain the association we report here between handedness and disease, with some diseases being more common and others less common in left-handers.

We have evaluated the concept of AD as "−2," largely because it is so poorly defined as to be virtually meaningless. Although handedness and language lateralization are at least modestly correlated, the evidence that the two are also correlated with the lateralization of spatial function is weak. Furthermore, researchers incorporate other variables, such as eyedness, footedness, and familial sinistrality, in their conceptualization of AD and move between categories of "left-handedness" and "non-right-handedness" in their search for significant effects. If one tries enough ways of classifying one's subjects, "significant" effects may well emerge (Bishop, 1990c).

All things considered, then, we find the evidence to support the Geschwind and Galaburda (1987) model lacking and would suggest that psychologists and physicians have more useful things to do than to carry out further assessments of the model. Most of the pertinent literature has concerned the relationship between handedness and immune disorder. It is only too easy to give some handedness questionnaire to a large sample of captive subjects, score it in an arbitrary way (see Bishop, 1990c), and then to ask about various atopic and immune disorders. This will frequently lead to a publishable paper, but perhaps not a useful one. Our meta-analyses suggest that the relations that do exist between handedness and immune disorder are not immunologically meaningful. This would lead us to argue that the effects are the consequence of some third variable. Perhaps the increased incidence of colitis in left-handers results from the stress of being left-handed in a right-hander's world (Coren, 1992), while the decreased incidence of myasthenia gravis and arthritis originates with some other source. Speculation may well be premature in any case in conditions such as ulcerative colitis and Crohn's disease, whose etiology is still obscure and controversial. While questions con-

cerning possible links to handedness might merit further investigation (and additional replication is still needed to confirm these effects), it must be accepted that they can hardly, in the context of the other findings, constitute a validation of the Geschwind hypothesis.

One problem is that the attractiveness and breadth of the Geschwind and Galaburda theory (1987) is such that it virtually requires a stronger model to drive it out (Kuhn, 1970). The present review indicates that the real problem lies in developing a model for the association between AD and language disorders. Certainly, major steps in this direction have been taken in the work of such authors as Bishop (1990a), Comings and Comings (1986), McManus and Bryden (1991, 1992, 1993), and Satz et al. (1985a).

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