Biological Factors in Attention Deficit-Hyperactivity Disorder

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For a number of years, clinicians and researchers have recognized the existence of a subgrouping of children who exhibit chronic and pervasive signs of inattention, impulsivity, and physical restlessness, as well as deficiencies in rule-governed behavior, which deviate significantly from age and gender expectations (Barkley; 1981; Ross & Ross, 1982; Wender, 1971). Since first being identified by Still (1902), this particular pattern of behavioral difficulties has undergone numerous changes in the diagnostic terminology used to describe it. Attention Deficit Disorder (with or without Hyperactivity), Hyperkinesis, Hyperkinetic Reaction of Childhood, Hyperactive Child Syndrome, Minimal Brain Damage, and Minimal Brain Dysfunction are some of the many labels that have been applied to this disorder in the past. With the arrival of the recently revised third edition of the Diagnostic and Statistical Manual (DSM III-R, American Psychiatric Association, 1987), this same behavioral constellation is now known as Attention Deficit-Hyperactivity Disorder (ADHD).

As is evident from an inspection of these earlier labels, references to specific biological factors have sometimes been included in the diagnostic terminology. This practice, of course, reflected the prevailing belief of the time—that such factors were presumed to be at the etiological core of ADHD children's behavioral difficulties. Although the present terminology, ADHD, does not include any such references, it would be a mistake to conclude that biological factors are no longer considered relevant in understanding the etiology of this disorder. On the contrary, in recent years investigators have focused a great deal of attention upon the potential etiological contributions of a large number and variety of biological circumstances, including neurological involvement, genetic transmission, and toxic reactions.

Thus far, this diverse line of scientific inquiry has not led to the identification of a specific etiological mechanism to account for ADHD symptomatology. Nevertheless, it has served to increase our understanding of the relationship between various biological factors and ADHD. In particular, there would appear to be an emerging consensus that biological factors are primarily responsible for the development of ADHD. The purpose of this paper is to provide an overview of the relevant research that has led to this consensus. While it is recognized that environmental factors also may contribute to the unique expression of this disorder in individual cases,

especially when secondary problems, such as oppositional and defiant behaviors are involved, a discussion of these matters is beyond the scope of this paper. Readers interested in learning more about this aspect of ADHD should consider reviewing other sources (e.g., Ross & Ross. 1982).

Neurological Factors

Throughout the long history of this clinical disorder, neurological factors have received the lions' share of the attention that has been directed to etiological concerns. As is often the case with other efforts to link organic factors to psychopathology, much of this neurological research has been plagued by methodological shortcomings, frequently related to sample selection problems, measurement difficulties, and ethical limitations. As a result, definitive statements about the existence of an etiological relationship between specific neurological factors and ADHD can not be made at the present time. What we do know about this relationship is summarized below.

Brain Damage. Alterations in neurologic structure have long been implicated in the etiology of ADHD. Based primarily upon observations of children recovering from encephalitis, head trauma, and other types of neurologic illness and injury, Still (1902) and others (Strauss & Lehtinen, 1947; Strecker & Ebaugh, 1924) postulated that ADHD symptoms resulted from gross brain damage. Years later, Pasamanick and Knobloch (1960) proposed that less severe forms of brain damage, resulting from bleeding during pregnancy, anoxia, and various other pre- and perinatal circumstances, might also contribute to a number of learning and behavioral disorders, including ADHD.

Evidence pertaining to this brain damage hypothesis comes from several sources. While there is some data to suggest that damage to certain parts of the brain, such as the prefrontal cortex, can lead to ADHD-like symptomatology (Heilman & Valenstein, 1979; Mattes, 1980; Taylor, 1986), it is clear that most children with well-documented brain damage do not exhibit ADHD problems (Rutter, 1977). Conversely, in studies that directly examined ADHD populations, less than 5 to 10% of these children were found to have histories suggestive of brain damage (Rutter, 1977; Stewart & Olds, 1973). Recently obtained computerized axial tomography (CAT) results also failed to reveal any significant neuroanatomical differences between ADD children and matched controls (Shaywitz, Shaywitz, Byrne, Cohen, & Rothman, 1983). Further contradictory evidence comes from two large prospective studies that followed children for several years beyond the prenatal period. In neither of these investigations was there strong evidence to support the contention that pre- and perinatal complications, which presumably lead to less severe forms of brain damage, were etiologically related to the presence of ADHD among school-aged children (Nichols & Chen, 1981; Werner & Smith, 1977). To account for recent findings supporting the contention that a potential relationship exists between pre- and perinatal complications and the emergence of ADHD symptoms in later childhood (Hartsough & Lambert, 1985), it is likely that biological mechanisms other than brain damage are involved. Given this overall pattern of results, the consensus among most investigators today is that while certain types of brain damage can lead to ADHD-like symptomatology, it clearly is not a major cause of ADHD (Barkley, 1981; Ross & Ross, 1982; Routh, 1978; Taylor, 1986).

Neurological Dysfunction. While brain damage may not be a primary cause of ADHD in most children, indirect evidence continues to accumulate, suggesting that brain function may be impaired to some degree in circumscribed cortical and subcortical areas. One line of evidence

supporting this assertion comes from a recent cerebral blood flow (CBF) study in which comparisons were made among ADHD children, normal children, and children with developmental dysphasia (Lou, Henriksen, & Bruhn, 1984). Because CBF has been shown to correlate positively with extent of neuronal function in target areas (Fox & Raichle, 1985), it therefore serves as an indirect marker for cerebral activity. Results obtained from the Lou et al. (1985) study demonstrated that the ADHD children had decreased blood flow in the central white matter of the frontal lobes and in the caudate nucleus, relative to the normal perfusion that was found in these same regions among the non-ADHD children. Of additional interest is that this hypoperfusion in the ADHD children improved with the administration of Ritalin. Results in line with these CBF findings recently were reported in a study using BEAM technology for computer averaging of EEG wave patterns during cognitive tasks (Satterfield, 1986). More specifically, decreased patterns of activation or reactivity were found in the frontal areas of ADHD children, relative to controls. Despite their apparent support for the existence of frontal and/or frontal-limbic dysfunction in ADHD children, these sorts of investigations require careful replication before much confidence can be placed in their conclusions.

A second line of evidence stems from studies of the performance of ADHD children on neuropsychological tasks sensitive to brain dysfunction. In one such study, ADHD children displayed deficits in their performance on the Wisconsin Card Sorting Task, which presumably measures frontal lobe functioning related to the use of environmental feedback in goal-directed behavior (Chelune, Ferguson, Koon, & Dickey, 1985). Further support comes from investigations in which ADHD children performed less well on measures of vigilance and impulse control (Douglas, 1983; Taylor, 1986), both of which have been shown to be quite sensitive to frontal lobe dysfunction. While these sorts of findings provide support for a brain dysfunction hypothesis, such support must be viewed as preliminary, until additional investigations, using larger and better defined ADHD samples, as well as a larger battery of frontal lobe measures, are completed.

A third line of evidence may be gleaned from the large number of psychophysiological studies of ADHD children that have been conducted over the past 15 years. In their extensive review of these investigations, which often rested upon assumptions of either over- or underarousal of the central nervous system (Bradley, 1937; Freibergs & Douglas, 1969; Laufer, Denhoff, & Solomons, 1957; Satterfield, Cantwell, & Satterfield, 1974), Hastings and Barkley (1978) uncovered a number of serious methodological problems that made it difficult to draw any definitive conclusions about either arousal theory. However, what consistency there was across different psychophysiological measures implied neither over- nor underarousal; instead, it suggested more of a pattern of under-reactivity to stimulation among ADHD children as compared with normal controls. Others reviewing this literature have reached similar, albeit tentative, conclusions (Callaway, Halliday, & Naylor, 1983; Ferguson & Pappas, 1979; Rosenthal & Allen, 1978).

Taken together, these three lines of indirect evidence regarding brain functioning among ADHD children would seem to indicate a pattern of under-reactivity in certain cortical and subcortical areas, particularly those involving the mesial frontal and frontal- limbic regions. Such findings clearly are in line with current models of brain functioning (Dimond, 1980; Lezak, 1983; Luria, 1973), which emphasize the role of the orbital and mesial surfaces of the pre-frontal cortex and

its rich interconnections with the limbic system in mediating the maintenance and inhibition of behavior, as well as the modification of behavior by environmental feedback. Although this line of theoretical reasoning is rather appealing, it is important to keep in mind that research in this area is in its infancy, with many studies yet to be replicated. Of additional concern is that the studies reviewed above often were limited in their internal validity by small sample sizes, poor definition of ADHD selection criteria for subjects, and often poorly system atized use and/or scoring of their dependent measures. Hence, it would appear prudent at present to view neurological dysfunction as a viable etiological explanation for ADHD, requiring further, carefully-controlled empirical examination.

Neurochemical Imbalances. In recent times additional attention has been directed to the possible causal role played by neurochemical imbalances and/or deficiencies, which in part may account for the aforementioned neurological dysfunction hypotheses. In particular, abnormalities in one or more of the monoaminergic systems (i.e., those involving serotonin, dopamine, and norepinephrine) have been implicated (Shaywitz, Shaywitz, Cohen, & Young, 1983; Wender, 1971). Much of the impetus for this line of reasoning stems from a consideration of the well-documented therapeutic benefits of various stimulant medications, such as Ritalin, which, by virtue of their chemical similarity, presumably compensate for monoamine irregularities. Despite the intuitive appeal of this theoretical rationale, definitive empirical support has been lacking. Of particular interest is the finding that normal children respond to stimulant medication in ways similar to that of ADHD children (Rapoport, Buchsbaum, Zahn, Weingartner, Ludlow, & Mikkelsen, 1978). This result by itself, of course, does not rule out the possibility of monoamine abnormalities in ADHD children, but it certainly does provide sufficient justification for questioning the use of stimulant drug responding as evidence for such abnormalities. In a more direct analysis of this matter, some investigators have reported results consistent with a neurochemical explanation, primarily involving either dopamine (Shaywitz, Cohen, & Bowers, 1977) or norepinephrine mechanisms (Shekim, Dekirmenjian, Chapel, Javaid, & Davis, 1979), while others have not (Rapoport, Quinn, & Lamprecht, 1974; Wender, Epstein, Kopin, & Gordon, 1971). Along with identifying a number of methodological limitations in such studies, recent reviews of this literature (Raskin, Shaywitz, Shaywitz, Anderson, & Cohen, 1984; Zametkin & Rapoport, 1986) have reached the conclusion, albeit somewhat tentatively, that dopamine and/or norepinephrine may be involved in the etiology of ADHD. Given that the mesial frontal and frontal-limbic areas of the brain presumably are mediated to a great extent by dopamine and/or norepinephrine mechanisms, these neurochemical findings would appear to be consistent with the previously discussed CBF hypoperfusion and BEAM underactivity results reported for ADHD children. However, until further, more rigorous research is completed, such conclusions should be regarded cautiously.

Neurological Immaturity. In a somewhat different vein Kinsbourne (1977) has proposed that ADHD may stem from neurological immaturity, rather than from neurological damage or dysfunction. As emphasized by Barkley (1985), this notion of immaturity is one that does not necessarily imply that ADHD children will outgrow their problems; in many cases, their behavioral control will improve over time but remain chronically delayed relative to same-aged peers. Because the locus of this hypothesized neurologic immaturity has not been clearly identified, much of the evidence pertaining to this potential etiological relationship emanates from indirect sources. Preliminary support comes from clinical investigations in which the

attention spans, impulse control, activity levels, and social interaction skills of ADHD children were found to be similar to those of younger normal children (Barkley, Karlsson, & Pollard, 1984; Cunningham. Siegel, & Offord, 1980; Loney, 1980). Additional empirical support stems from studies in which ADHD children displayed EEG and evoked potential patterns suggestive of immature cortical activity (Buchsbaum & Wender, 1973; Hastings & Barkley, 1978; Surwillo, 1977). The presence of an increased number of neurological soft signs among ADHD children (Casey, 1977) also has been cited by some investigators as an indication of neurological immaturity. Other investigators, however, either have not found this result or have questioned its clinical significance when present (Ferguson & Rapoport, 1983). Hence, despite its appeal, this notion of neurological immaturity is one that must await more direct empirical support, prior to drawing more definitive conclusions about its relationship to ADHD.

Genetic Factors

The etiological relationship between genetic factors and ADHD is one that has received increased consideration in recent times. Most of the research in this area has involved comparisons of the incidence of ADHD among children and their biological and/or adoptive relatives. Despite numerous methodological shortcomings, including small sample sizes, inadequate comparison groups, and retrospective diagnoses of ADHD, many of these investigations have produced evidence consistent with a genetic hypothesis.

Family Studies. One source of support for this hypothesis comes from studies in which comparisons were made between the families of ADHD and normal children. Such investigations generally have found an increased incidence of retrospectively diagnosed ADHD, as well as higher rates of alcoholism, affective disorder, and other psychiatric difficulties, among the natural parents and extended relatives of the ADHD children (Biederman, Munir, Knee, Armentano, Waternaux, & Tsuang, 1987; Cantwell, 1972; Morrison, 1980). Similar differences have been reported in comparisons between biological and adoptive families of ADHD children (Alberts-Corusch, Firestone, & Goodman, 1986; Cantwell, 1975; Morrison & Stewart, 1973). A useful illustration of the magnitude of such differences is evident in the recently reported research of Deutsch (1987), who found that between 21 and 25% of the natural parents of well-defined ADHD children also had histories of ADHD themselves versus the 4% incidence of ADHD that was detected among the adoptive parents of ADHD children. Although these results would seem to support the contention of a genetic link to ADHD, some investigators have questioned the specificity of any such connection (Ross & Ross, 1982), given that similar familial patterns have been detected among other behavior-disordered populations (Stewart & Leone, 1978).

Sibling Studies. A small number of studies utilizing sibling comparisons also has provided some degree of support for a genetic explanation. In one such research endeavor, a significantly greater incidence of ADHD was found among full siblings of ADHD children, relative to half siblings (Safer, 1973). More recently, Pauls and his associates (Pauls, Shaywitz, Kramer, Shaywitz, & Cohen, 1986) evaluated the families of 72 ADHD children and calculated the risk of siblings having this disorder, taking into account whether or not there was a parental history of ADHD. The results obtained from this line of research revealed a significantly greater sibling risk for ADHD when there was a parental history of ADHD (.34 versus .11 for unaffected parents), especially in the case of female ADHD probands (.54 versus .15 for unaffected parents). Such

results were interpreted as support for a direct vertical transmission of ADHD, with the gender of the child moderating this genetic effect. Sibling comparisons also have been conducted in the context of twin investigations. Although hindered by very small numbers of subjects, such studies generally have found higher ADHD concordance rates among monozygotic twins than among dizygotic twins (Heffron, Martin, & Welsh, 1984; Lopez, 1965; McMahon, 1980), which is in line with genetic predictions.

As noted throughout the preceding discussion, most of the available research in this area has been beset by methodological shortcomings, which limits the validity of any conclusions that might be drawn. More convincing support for a genetic hypothesis must come from future research studies that incorporate tighter methodological controls. In addition, relatively more direct investigations of this matter, such as those involving chromosomal analyses, must be completed prior to drawing any definitive conclusions. In the meantime, the currently available research findings would seem to suggest that the genetic transmission of ADHD is a promising hypothesis in need of further empirical validation.

Toxic Reactions

It is only in recent years that investigators have raised the possibility that toxins may play a role in the etiology of ADHD. While several toxins have been implicated, only a few have received what might be considered adequate empirical support to warrant further serious consideration.

Dietary Factors. Feingold's (Feingold, 1975) assertion about the behavioral effects of artificial food additives is perhaps the most widely known of all the toxin hypotheses that have been put forth to date. In particular, Feingold has contended that more than 50% of all ADHD children develop their symptoms as a result of adverse reactions to food additives. Contrary to popular opinion, there is very little empirical evidence to substantiate the claim that ingestion of food additives leads to clinical levels of ADHD among normal children or that it significantly exacerbates the behavioral problems of children already manifesting ADHD symptoms (Conners, 1980; Gross, Tofanelli, Butzirus, & Snodgrass, 1987; Taylor, 1979). Another commonly held belief today is that ADHD symptoms stem from the ingestion of refined sugar (Prinz, Roberts, & Hantman, 1980). Despite its persistent popularity, this etiological explanation also has fared poorly under the scrutiny of carefully controlled studies in which double-blind, placebo conditions were employed (Barling & Bullen, 1985; Milich, Lindgren, & Wolraich, 1986; Milich & Pelham, 1986). The ingestion of high doses of food dyes is another dietary factor that has been proposed as an etiological mechanism. While there has been some support for the existence of a relationship between food dyes and performance on a sustained attention task (Swanson & Kinsbourne, 1980), most investigators today agree that the etiological contribution of food dyes is relatively minor, occurring in only a very small percentage of the children diagnosed as ADHD (Barkley, 1985; Ferguson & Rapoport, 1983). Food allergies (Taylor, 1980) and vitamin deficiencies (Brenner, 1982; Smith, 1976) have been implicated as well, but neither of these factors has received sufficient empirical attention to warrant identification as etiological mechanisms at the present time (Haslam, Dalby, & Rademaker, 1984).

Lead Poisoning. Increased body-lead burden, often stemming from ingestion of lead-based paints and from inhalation of lead fumes in the atmosphere, is yet another toxic condition that has been associated with ADHD symptomatology. Although there has been at least one study

that failed to find any such etiological connection (Milar, Schroeder, Mushak, & Boone, 1981), most of the pertinent research in this area has produced findings supporting the view that elevated lead levels are associated with ADHD (Baloh, Sturm, Green, & Gleser, 1975; David, Clark, & Voeller, 1972; Gittelman & Eskenazi, 1983; Marlowe et al., 1985). As summarized by Ross and Ross (1982) in their excellent discussion of the theoretical and empirical aspects of this matter, the presumed link between ADHD and elevated lead levels is one that certainly warrants further serious consideration.

Anticonvulsant Medications. Recent studies have suggested that certain anticonvulsant medications, such as phenobarbital and Dilantin, can produce ADHD symptoms as side effects when used in the treatment of childhood epilepsy (Wolf & Forsythe, 1978). Such a finding is of special theoretical interest, when one considers that the sedative properties of these medications may lead to cortical under-reactivity, which in an earlier section of this paper was identified. as having a relationship, albeit a tentative one, with ADHD. Despite the intuitive appeal of this theoretical speculation, the etiological relevance of this type of toxic reaction must be viewed as quite limited, given that most ADHD children typically do not take these medications. Consequently, the significance of these findings exists mainly for those professionals who treat behavioral disorders in epileptic children, especially when there are concerns about the potential development or worsening of ADHD symptoms, following the initiation of anticonvulsant medication therapy.

Maternal Toxic Exposure. Accumulating slowly are findings suggesting that maternal exposure to nicotine (Denson, Nanson, & McWaters, 1975) and alcohol (Shaywitz, Cohen, & Shaywitz, 1980) during pregnancy may be related to an increased incidence of ADHD among the children of these pregnancies. As noted by Spranger (1981), these early studies were limited by their retrospective assessment of maternal smoking and alcohol use among already diagnosed ADHD populations. More recent prospective studies, however, have continued to underscore this suspected link. Of particular interest are the large-scale prospective studies of Streissguth and her colleagues, who followed more than 1,500 women through their pregnancies up until the time their children were 7 years of age (Streissguth, Barr, Sampson, Parrish-Johnson, Kirchner, & Martin, in press; Streissguth, Martin, Barr, Sandman, Kirchner, & Darby, 1984; Streissguth, Martin, Martin, & Barr, 1981). Such investigations consistently have revealed significant associations between levels of maternal smoking/alcohol consumption and the degree to which offspring displayed later difficulties with sustained attention, hyperactivity, and task organization.

In review, the available research findings would seem to suggest that elevated lead levels, anticonvulsant medications, and maternal exposure to nicotine and alcohol during pregnancy may give rise to ADHD symptoms or exacerbate such problems in children with preexisting ADHD. Whether or not these associations are etiological in nature cannot be determined at the present time. In order to make such a determination, additional theoretical analysis and research are needed. In particular, attention must be focused upon the specific biological pathways by which toxins presumably lead to ADHD-like behavior.

Other Etiological Considerations

Minor Physical Anomalies. Several investigators have called attention to the apparently higher incidence of minor physical anomalies (MPA) among ADHD children, relative to normal children (Firestone, Peters, Rivier, & Knights, 1978; Rapoport & Quinn, 1975). As might be expected, this finding has led to further speculation about the relationship between biological factors and ADHD. Some have explained this association on the basis of genetic considerations (Firestone et al., 1978). Others have speculated that intrauterine complications, especially during the first trimester, might be involved (Rapoport & Quinn, 1975). More recently, Firestone and Prabhu (1983) reported that a genetic predisposition to MPA, in combination with a history of obstetrical complications, greatly increased the accuracy of predicting that a child would manifest ADHD problems. As has been noted by Ferguson and Rapoport (1983), this type of relationship is not necessarily specific to ADHD children. Increased frequencies of MPA also have been found among children with other types of behavioral problems, as well as among learning disabled and autistic populations (Campbell, Geller, Small, Petti, & Ferris, 1978; Gualtieri, Adams, Shen, & Loiselle, 1982; Steg & Rapoport, 1975). Consequently, while there is ample evidence from the MPA literature to suggest that a relationship between biological factors and ADHD exists, the exact etiological significance of this relationship remains uncertain at present.

Biological Variation. Implicit in many of the previously reviewed etiological accounts is the idea that structural and/or functional abnormalities are the cause of ADHD. An alternative to this viewpoint is the notion of biological variation (Kinsbourne, 1977), which is based upon an assumption of differences, rather than deficits, across children. Fundamental to this perspective is the idea that children display observable differences in temperamental style from birth (Wender, 1987). If one were to measure these inborn temperamental characteristics across the population, they presumably would be distributed in a normal or bell-shaped manner, as are various other characteristics, including intelligence and physical size. On the basis of statistical considerations alone, those children with levels of sustained attention, impulse control, and physical restlessness that lie at the extreme lower end of this distribution would be considered deviant. In more practical terms, these same children would be much more likely to encounter difficulties in meeting behavioral expectations both at home and at school, which in turn would increase their chances for experiencing negative interactions with peers and adults. Such difficulties might then be labeled ADHD, primarily on the basis of the degree to which they deviate from the norm. Thus far, this notion of biological variation is one that has not received a great deal of empirical attention. As might be expected, there are numerous difficulties inherent in evaluating this sort of hypothesis, primarily because it rests upon an assumption of inborn temperamental differences across children, the causes of which are unknown. De spite such limitations, it remains an interesting and viable alternative to the vast majority of etiological explanations, which emphasize biological deficit notions.

Summary and Conclusions

As is evident from the preceding review, a large number and variety of biological circumstances have been implicated in the etiology of ADHD. Many of these, including neurological damage and the ingestion of food additives and sugar, have not held up well under close scientific scrutiny. Others, such as those pertaining to genetic transmission, biological variation of inborn temperamental differences, mesial frontal and frontal-limbic dysfunction, elevated lead levels,

and prenatal exposure to nicotine and alcohol, have received sufficient theoretical and empirical support to warrant further serious consideration as etiological mechanisms.

This latter finding is of special interest, because it raises an important question: How does one account for the fact that so many biological circumstances appear to be involved in the etiology of ADHD? There would seem to be at least two possible answers to this question. First of all, it may be the case that many of these biological circumstances are interrelated, rather than independent of one another. In this context they may be viewed as part of a sequence of biological events, which ultimately leads to ADHD. This notion of interrelatedness is one that was highlighted in several sections of the preceding review. For example, it was noted earlier that suspected dopamine and/or norepinephrine abnormalities may underlie reported deficiencies in mesial frontal and/or frontal-limbic system functioning, which in turn may lead to the appearance of ADHD. In view of the preliminary support that it has received, genetic transmission also may play a role earlier in this same sequence.

Along with this notion of interrelatedness, it is necessary to consider the possibility that the etiology of ADHD is multidimensional, rather than unidimensional, in nature. In this regard ADHD may stem from any one or combination of several causal factors, all of which share a final common pathway leading to ADHD symptomatology. To pursue this line of theoretical reasoning one step further, it also may be the case that some factors account for a greater percentage of the ADHD population than others. Based upon the preceding review, for example, it would not be unreasonable to consider the possibility that genetic transmission, biological variation of inborn temperamental differences, and neurological dysfunction account for the majority of ADHD cases, whereas elevated lead levels, prenatal exposure to nicotine and alcohol, food dyes, and focal brain damage lead to ADHD in only a very small percentage of this population.

Working from these assumptions, Barkley (1985) recently proposed that the pattern of causality in ADHD may parallel that found in mental retardation. More specifically, the suspected multiple causes of ADHD presumably lead to an uneven, bimodal distribution of ADHD symptoms. The larger of these two overlapping distributions reflects the phenotypic variation of ADHD within the population. In line with the notion of biological variation, those children at the extreme lower end of this distribution would be labeled ADHD, primarily because they deviate from the norm to a degree that leads to interpersonal conflict and maladjustment. Hypothetically reflected by the smaller of the two overlapping distributions are those children whose ADHD stems from any one or c^{o}mbination of the various biological circumstances discussed earlier, such as neurological dysfunction, elevated lead levels, and prenatal exposure to toxins.

What should be evident from the discussion thus far is that while much etiological progress has been made recently, there clearly is a need for further research. In conducting such research, future investigators must try to avoid many of the methodological shortcomings that have plagued the field to date. While it certainly is not the purpose of this paper to provide a lengthy discussion of these methodological concerns, there are several frequently encountered methodological problems in this research literature that bear mentioning.

An especially common problem is the inadequate manner in which ADHD populations are defined. In part, this stems from a consideration of the different labels (e.g., Minimal Brain Damage) that have been used to describe this population. In a number of recent investigations, researchers have continued to use obsolete diagnostic terminology and criteria, which only serve to hinder comparisons with other studies. Closer adherence to the diagnostic criteria set forth in DSM III-R would go a long way towards reducing this type of difficulty. Another sample definition problem may be found in studies that failed to take into account that ADHD is a disorder that may vary a great deal in severity. As those who work with this population well know, this is an important clinical distinction to make. The inclusion of severity ratings in DSM III-R is likely to facilitate attention to this matter, thereby insuring more accurate cross-study comparisons. Also problematic is the frequent lack of methodological control over the presence of associated behavioral and emotional difficulties, such as conduct problems and depression. Failure to monitor these types of difficulties increases the likelihood of drawing faulty inferences across studies that claim to have examined similar populations. To eliminate this sort of problem, it is essential that investigators make an effort to monitor the potential impact of these associated disorders.

Along with these sample definition problems, it is not uncommon. to find an excessive reliance upon correlational designs in this research literature. While this by itself is not a problem, many investigators make the mistake of inferring causality whenever associations between biological circumstances and ADHD- like behaviors are found. This type of faulty reasoning is readily apparent in the recent contention that ingestion of sugar leads to ADHD-like behavior. As has been shown repeatedly in several double blind studies, the apparent association between sugar and ADHD is not causal in nature. Instead, the co-occurrence of these two circumstances would seem to stem from their relationship to a third factor, which in this case may be child and/or adult expectations about the likely impact of sugar upon their behavior. As a general rule it is important for investigators to keep in mind that the co-occurrence of two events is not sufficient grounds for establishing a causal link between them. It is, however, sufficient for speculating that a causal relationship may exist, which must then **be** explored further by means of more direct experimental analysis.

Another frequently encountered methodological problem is an error in logical thinking, known as affirming the consequent. This error occurs whenever investigators reverse the direction of a conditional, if-then, sequence. It is based upon the faulty assumption that if A leads to B, then the presence of B implies the presence of A. This sort of error in logical thinking is readily apparent in many of the early efforts to account for the etiology of ADHD. More specifically, because neurological damage sometimes led to ADHD-like problems, it was inferred that the presence of ADHD stemmed from neurological damage. As was noted earlier, there is relatively little empirical evidence to support the contention that neurological damage is a major cause of ADHD. In line with the advice that was given with respect to drawing inferences from cor-relations, investigators would be well advised to avoid inferring causal relations on the basis of this type of logical reasoning.

In reviewing these sorts of methodological problems it is not the intent of this paper to imply that they are in any way specific to the research that has examined the relationship between various biological factors and ADHD. On the contrary, these same sorts of methodological problems

may be found in many other areas of empirical investigation. The main reason for calling attention to them presently is to alert investigators to some of the avoidable pitfalls that have impeded efforts to increase our theoretical understanding of the etiology of ADHD.

In addition to attending to these methodological concerns, in- vestigators may wish to consider conducting research that systematically examines various combinations of suspected etiological mechanisms. While this may not always be possible for practical reasons**,** this type of empirical effort would go a long way towards clarifying the degree to which various biological factors are interrelated. For example, it would be especially interesting to examine the etiological contribution of genetic transmission in a study that also focused upon neurological dysfunction.

In sum, in order to clarify the extent to which biological factors are involved in the etiology of ADHD, additional well-controlled research must be completed. In the meantime, it must suffice to conclude that while there is ample evidence to suspect the existence of a relationship between biological factors and ADHD, the exact nature of this relationship is one that is not entirely clear.

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