Prediction of Stimulant Response in Children with ADHD

by

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ABSTRACT

Stimulant drugs often have a profound calming effect on overactive and inattentive behaviors in children with attention deficit-hyperactivity disorder (ADHD), but only approximately 75 per cent of these children respond favorably to this treatment (Barkley, 1977). Discrimination of "responding" and "non-responding" groups on the basis of demographic, neurophysiological, or behavioral variables would be beneficial both for clinical (elimination of drug trial) and theoretical (description of subtypes) reasons.

Previous researchers have identified many promising predictor variables, but relationshps between predictor and criterion variables have generally been modest (although statistically significant) in size, and criterion variables have been poorly delineated. In addition, few multivariate investigations have been reported which take into account the relative predictive weight of these variables.

The present study evaluated the multivariate relationship between several predictor variables and response to medication in 336 ADHD children, as measured through both rating scales and longer-term outcome measures. Multiple regression analyses revealed that measures of inattention and overactivity were the best predictors of response to a double-blind stimulant medication trial, as determined through parent and teacher rating scales. For cases in which rating scale data were not available,

discriminant function analyses for "yes" versus "no" responders were also carried out, indicating results similar to those above. These relationships were highly significant but have limited clinical utility. Demographic variables were generally unsuccessful at prediction of medication response.

Additional findings indicated that the results of the clinical trial (as determined by parent and teacher behavioral ratings) were not strongly related to ultimate placement on medication. Further exploration of this issue is called for.

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DEDICATION

To my family

for their years of patience and support

PART A

INTRODUCTION

I. OVERVIEW

Since Bradley (1937) first identified a beneficial, calming effect of stimulant drugs on children with hyperactive behaviors, stimulants have steadily become the treatment of choice for children with Attention-Deficit Hyperactivity Disorder (ADHD) (DSM-III-R, American Psychiatric Association, 1987). Recent estimates indicate that 3 to 5% of school-aged children are diagnosed as ADHD (Barkley, 1990), and a steady increase in the use of stimulant medication treatment exists. An estimated 6% of public elementary school students were prescribed stimulants in 1988, with a consistent doubling of the rate of medication treatment every four to seven years since 1971 (Safer & Krager, 1988). Accordingly, research on the efficacy, potential side effects, and long-term outcome of stimulant treatment have become increasingly relevant.

Research on efficacy has demonstrated that not all children respond favorably to drug treatment. A comprehensive review of stimulant drug research (Barkley, 1977) indicated that an average of 75% of these children responded well to this treatment, while 25% did not change or demonstrated exacerbated behavioral symptoms. Given that not all children respond favorably to stimulant medication, it would be clinically and theoretically valuable to determine which factors would discriminate responders (those

that respond well to drug treatment) from non-responders (those whose behavior is unchanged or exacerbated with drug treatment). If reliable a priori discrimination of these groups were possible, not all ADHD children would need to submit to an actual drug trial. Additionally, and perhaps more importantly, identification of variables for reliable discrimination between these groups may provide critical information with regard to the underlying mechanism(s) of ADHD.

Findings in this regard would also contribute substantially to the existing ADHD subtyping literature. Since ADHD children present with widely varying symptomatology, much of the recent ADHD research has attempted to categorize these children into meaningful subgroups. These attempts have included subtyping on the basis of degree of hyperactivity, aggression, internalizing symptoms, and situational nature of symptomatology (Barkley, 1990). To date, the research has been equivocal with regard to identification of the most meaningful subgrouping approach, and more research is called for in this area. A potential subtyping of ADHD children includes "responders" and "non-responders", particularly if useful variables are distinctly associated with each group (Barkley, 1990). This study will attempt a further understanding of responders versus non-responders through identification of those variables reliably associated with each group.

II. PROBLEMS WITH THE EXISTING ADHD LITERATURE

Previous attempts at identification of reliable discriminating variables have yielded highly inconsistent results, as the following chapter (III. Prediction of Stimulant Response) indicates. This inconsistency is likely due to a number of difficulties within the vast, existing ADHD literature. In order to more fully understand prior research with regard to stimulant response, these overall problems within the ADHD literature must be addressed.

A. CONCEPTUALIZATION OF THE ADHD SYNDROME

A critical evaluation of existing ADHD literature with regard to stimulant response is riddled by continually shifting conceptualizations of what constitutes the ADHD child. These changes have resulted in a body of literature on a variety of samples, from children whose symptoms range from overactivity alone to those with the full syndrome conceptualized today as ADHD. These children, who may demonstrate a variety of deficits in attentional skills, impulse control, activity level, and psychosocial skills, were first termed "organically driven" (Kahn & Cohen, 1934), then "minimally brain dysfunctional" by Strauss and Lehtinen (1947). Although an organic etiology was assumed, little evidence was provided in support of this assumption (Rutter, 1982). Nevertheless, several decades of research was

carried out on populations of children for whom organic etiology, attention deficit, and inadequate impulse control may or may not have been present.

With a shift in conceptualization from undifferentiated brain dysfunction to movement disorder came the Hyperkinetic Reaction of Childhood (DSM-II, American Psychiatric Association, 1968). This nosology characterized the ADHD child as one with excessive and inappropriate activity levels. Hence, research during this period focused on "squirmy" and active children, and not necessarily on children with the full range of symptoms conceptualized today as ADHD.

The work of Virginia Douglas and her colleagues (Douglas, 1972, 1980a, 1980b, 1983; Douglas & Parry, 1983; Douglas & Peters, 1979) was central to the most recent shift in conceptualization, in which cognitive as well as movement dysfunction was considered integral to the disorder. Two constructs, impulsivity and attentional difficulty, were added along with overactivity to further delineate this syndrome. The change from Hyperkinesis to Attention Deficit Disorder with or without Hyperactivity (DSM-III, American Psychiatric Association, 1980) reflects this modification. Although similar to the most recent nosology, the distinction between the presence or absence of hyperactivity also generated different samples than those identified currently.

With the current conceptualization of Attention Deficit-Hyperactivity Disorder (DSM-III-R, American Psychiatric Association, 1987), hyperactivity is again considered central to the disorder.

These historical differences in population definition have led to difficulties with regard to comparability. It is unlikely that a 1972 research study regarding medication effects in children with "hyperactivity" is comparable to one carried out in 1992 in children with "ADHD". For example, degree of attention deficit (as opposed to quantity or quality of movement disorder) might hypothetically predict response to stimulant medication treatment. If children with primary attentional difficulties were not included in early stimulant prediction studies, this effect would not have been ascertained.

B. COMORBIDITY

In a recent review (Biederman, Newcorn, & Sprich, 1991), the literature was reported to "support considerable comorbidity of ADHD with conduct disorder, oppositional defiant disorder, mood disorders, anxiety disorders, learning disabilities, and other disorders, such as mental retardation..." (p. 564). The overlap of ADHD with conduct disorder is particularly pronounced, with rates of comorbidity reported at roughly 50% in clinic-referred samples (Biederman, Munir, & Knee, 1987; Hamden-Allen,

Stewart, & Beeghly, 1989; Munir, Biederman, & Knee, 1987; Szatmari, Boyle, & Offord, 1989). The marked presence of coexisting disorders (not controlled for in the majority of studies) also results in difficulties with comparability across research investigations. This is particularly true with regard to the present topic, since comorbidity could hypothetically have a differential effect on stimulant response.

C. DRUG ADMINISTRATION

Review of studies with regard to prediction of medication response also reveals wide differences in drug administration. Different drugs (amphetamine, dextro-amphetamine sulphate, methylphenidate hydrochloride, magnesium pemoline) and dosage schedules (low to high, fixed to flexible) have been utilized throughout these investigations. Although it is not possible to ascertain the precise impact of these variations, it is certainly likely that these inconsistencies differentially affected outcome. Since numerous investigators have reported increased improvement in behavior rating scales and cognitive performance as a function of stimulant dosage (Douglas, Barr, Amin, O'Neill, & Britton, 1988; Rapport, DuPaul, Stoner, & Jones, 1986; Winsberg, Kupietz, Sverg, Hungund, & Young, 1982), ineffective stimulant dosage could certainly mask a child's "good" response to the medication trial.

Also, evidence first reported by Sprague and Sleator (1977) and replicated by Brown and Sleator (1979) indicating that small doses of methylphenidate enhanced learning but did not improve social behavior, while larger doses improved social behavior but impaired learning, would seem to be directly associated with contradictory findings in research regarding drug effects.

In addition, drug trials were not consistently double-blind, placebo-controlled, or of a common duration. Given a high percentage of placebo responders in this population (Safer & Allen, 1976; Ullman & Sleator, 1986), the lack of a placebo trial would likely identify many children as "good" responders who might have responded equally well to a placebo.

D. PREDICTION VARIABLES

A wide variety of variables have been utilized in many different research investigations attempting to predict stimulant response, with an isolated variable's predictive validity often reported (e.g., electroencephalogram). Unfortunately, few multivariate investigations have been reported which take into account the relative weight of many predictors. Therefore, it is unclear to what extent each variable is significant when evaluated relative to other predictors. In addition, interactions between variables have not been evaluated.

E. OUTCOME MEASURES

Variables used to measure a subject's response to the medication trial have also varied considerably throughout the course of the present literature. The use by previous researchers of a variety of different indices to measure outcome has undoubtedly been a substantial factor contributing to the inconsistency in findings with regard to identification of effective predictor variables. Since measures of "good" vs. "poor" response are so widely variant, it is not surprising that differing results with regard to response will emerge. Measures previously utilized have included changes in physical activity level, scores on tests of achievement, intelligence or ability, and teacher or parent behavior rating scales. In some instances, the specific criteria for "good" or "poor" outcome are, in fact, often not detailed at all but are left to the subjective, post-hoc rating of the researcher. Some consistency with regard to an appropriate outcome measure is plainly called for.

Activity Level. With regard to activity level, it has been found that changes are significantly related to situational factors. In unstructured situations, ADHD children are not necessarily more active than non-ADHD children, and the administration of stimulant medication does not lead to a difference in activity level in playroom or home settings (Kaspar, Millichap, Backus, Child, &

Schulman, 1971; Kenny, Clemmens, Hudson, Lentz, Cicci, & Nair, 1971; Rapoport, Quinn, Bradbard, Riddle, & Brooks, 1974, Sleator & von Neumann, 1974). However, ADHD children generally demonstrate more motor activity in structured, task-oriented situations (Juiliano, 1974; Sykes, Douglas, Weiss, & Minde, 1971). Sleator and von Neumann (1974) also reported that while stimulant medication did not reduce playroom activity in ADHD children, it did reduce seat movement while these children were working on a learning task. Thus, the setting must be controlled for when utilizing activity level outcome measures, a variable which is often not discussed in the stimulant response literature.

Further research has also demonstrated that appropriateness of response, rather than activity level per se, may be a more adequate outcome measure (Whalen & Henker, 1976). The goal is for better integrated, more controlled motor behavior (less impulsive, more accurate) rather than simple quantitative reductions in activity rates or levels (Conrad, 1972).

In any case, with the shift in conceptualization of the ADHD syndrome from hyperactivity to inattention, activity level is no longer considered the sole target of stimulant medication treatment. It is therefore inappropriate as the sole measure of outcome.

Achievement and Intelligence Measures. Changes in achievement or intelligence have also been utilized to

measure response to stimulant medication in ADHD children. Results have been equivocal, but predominantly unsupportive, regarding a beneficial effect of stimulant medication on standardized achievement or intelligence test scores (Barkley, 1977). Improvement in scores reported in some studies is likely due to increased attentional behaviors rather than changes in basic intellectual or cognitive thought processes. Thus, although several researchers have utilized achievement indices to measure outcome, using these types of tests appears to be at best only an indirect or secondary measure of stimulant response.

Rating Scales. The majority of researchers have utilized changes in behavior rating scales to measure responsiveness to stimulant medication. These scales measure parents' and/or teachers' perceptions of the child's hyperactive and inattentive behaviors and, although they have been criticized for their subjectivity (Evans & Nelson, 1986 and Foster & Cone, 1986), they have reliably been found to improve among blind-raters in response to drug treatment (e.g., Abikoff & Gittelman, 1985; Sprague & Sleator, 1977; Varley & Trupin, 1983; Whalen & Henker, 1986). Rating scales have thus become the most frequently used measure for the determination of outcome.

While measures of outcome via rating scales are integral to the determination of immediate stimulant responsiveness, perhaps the most important measure of

outcome is that of longer-term adjustment. Unfortunately, this information is not available when rating scales are utilized as a sole outcome measure. A combination of behavior rating scales and long-term follow-up would therefore appear to be the most appropriate outcome measure.

Perhaps the most important issue regarding outcome, however, arises from children's variable response to stimulants. A specific "effect", uniformly demonstrable on measures of attention or behavior ratings, has not been demonstrated. In fact, children have been shown to respond variably to stimulants (Ross & Ross, 1982), and heterogeneity exists even within children across tasks (Douglas et al., 1988; Rapport et al., 1986). This leads to obvious difficulties with regard to the utilization of a single outcome measure across all ADHD children.

III. PREDICTION OF STIMULANT RESPONSE

Although the difficulties within this literature are evident, the existing literature with regard to prediction of stimulant repsonse is reviewed.

A. NEUROLOGICAL PREDICTORS

A difference in neurological mechanisms between responders and non-responders has long been hypothesized.

Neurophysiological Predictors. The paradoxical fact that stimulant medication is effective in calming ADHD children led to a popular theory regarding the etiology of ADHD. This theory stated that ADHD children have "underaroused" neural mechanisms; hence, the utilization of stimulant medication serves to "normalize" these children's responses to stimuli. Satterfield and Dawson's (1971) electrophysiological work was the pioneering research in this area.

Since only a subset of ADHD children respond to stimulant medication, several investigators have hypothesized that neurophysiological data would discriminate between responders and non-responders (i.e., that those who demonstrate underarousal through various neurophysiological measures would respond best to stimulants). Satterfield, Cantwell, Saul, Lesser, and Podosin (1973) provided preliminary support for this hypothesis. In their sample,

those ADHD children with abnormal EEGs and slowed orienting responses had significantly more improvement to methylphenidate treatment than subjects without abnormalities. (See Table 1 for a summary of prediction studies, including information regarding sample definition and measures used to indicate "improvement.")

Subsequent investigators have attempted to validate and extend Satterfield et al.'s (1973) work. Buschbaum and Wender (1973) compared the average evoked potentials (AEPs) of responders and non-responders, and found that the responders tended to deviate more from normal AEPs than did nonresponders. When given stimulant medication, the responders became more like normals while the nonresponders moved in the opposite direction. Halliday, Rosenthal, Naylor, and Callaway (1976) also reported an abnormal AEP in responders that was normalized with stimulants, while nonresponders demonstrated an abnormalizing effect. In a subsequent study, Halliday, Callaway, and Rosenthal (1980) validated their earlier results with the utilization of a prospective design.

Ferguson, Simpson, and Trites (1976) found that responders had lower-amplitude skin conductance orienting responses than did nonresponders, but did not find differences in reaction time or heart rate. They attribute this failure to wholly support the "underarousal theory" as perhaps due to differences in group definition.

Table 1

Summary of Research on Prediction of Stimulant Response in ADHD Children

Author(s) and Year	Sample Composition	Drug Administration and Outcome Measure(s)
Aman, Marks, Turbott, Wilsher, Merry (1991)	30 children attending special classes, meeting DSM-III criteria for ADD-H, with IQs from immeasurable to 90	Double-blind, three week trial (one wk. methylphenidate [MPD], one wk. thioridazine, one wk. placebo) Teacher and Parent ratings, cardiovascular measures, weight, side effects, IQ, attention task
Barkley, Cunningham (1979)	20 boys "previously diagnosed as hyperactive by their pediatricians"	One week MPD, one week placebo Observation of mother-child interactions, actometer
Barkley, Jackson (1977)	12 boys "diagnosed as hyperkinetic by local pediatricians and placed on methylphenidate"; 12 normal controls	All had been previously placed on MPD and were judged by their physicians to be "good responders" Heart rate, respiration, GSR

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Barkley, McMurray, Edelbrock, Robbins (1989)	74 children diagnosed as ADHD through DSM-III-R based on parent or teacher report, > 93rd percentile on hyperactivity scale of CBCL, IQ > 80, free of gross motor or sensory deficits, tics, seizures, gross brain damage, autism, or psychosis; further divided into groups on basis of T > or < 70 on aggression scale of CBCL	Double-blind, approximately three-week trial (one wk. .3 mg MPD, one wk. .5 mg MPD, one wk. placebo) Parent and teacher ratings, academic and attention tests
Buschbaum, Wender (1973)	24 children with a diagnosis of "MBD" as determined by two child psychiatrists, IQ > 80, absence of gross neurological disease, absence of psychosis	All children placed on MPD; response determined by rating of second author AEP
Conrad, Insel (1967)	31 children "seen for evaluation and eventually placed on amphetamine therapy"	All children previously placed on MPD Chart review, telephone interview with parents
Epstein, Lasagna, Conners, Rodriguez (1968)	10 children referred for restlessness, hyperactivity, poor concentration span and inadequate school performance	Double-blind four-week trial (two wks. .5 mg MPD, two wks. placebo)

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Epstein, Lasagna, Conners, Rodriguez (1968) (cont).		Pulse, respiration, fine motor coordination, Porteus Maze, WISC, parental report, neurological exam
Ferguson, Simpson, Trites (1976)	Hyperactive boys (N not reported)	All children previously placed on MPD Parent and/or physician judgment
Ferguson and Trites (1980)	79 boys with IQ > 80, no "obvious brain damage," diagnosed as ADD through Conners ratings and history	Double-blind, three-week trial (two wks .5 mg MPD, one wk MPD) Attention task, Parent and Teacher Conners, subjective rating
Gualtieri, Hicks (1985)	"24 hyperactive or conduct-disordered boys and girls"	Double-blind, three-week trial (one wk. .3 mg MPD, one wk. .6 mg MPD, one wk. placebo) Memory task, CCPT, seat movement, motor task, teacher behavior rating

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Halliday, Callaway, Rosenthal (1984)	20 children clinically judged hyperactive by specified criteria, Teacher Conners, normal IQ, neither psychotic or neurologically impaired, good physical health, living with at least one parent	See Halliday et al. (1980)
Halliday, Gnauck, Rosenthal, McKibben, Callaway (1980)	15 boys diagnosed hyperactive by referring pediatricians	Double-blind, twelve-week trial (three weeks each of .16 mg MPD, .33 mg MPD, .66 mg MPD, and placebo) Teacher Conners, academic performance, parent rating
Halliday, Rosenthal, Naylor, Callaway (1976)	17 boys with pervasive hyperactivity by observation or parental report, no concurrent medical problem, also reported by teacher to interfere with academic performance	Initial period to establish optimal dosage, then five or ten day double-blind trial of MPD and placebo Parent and Teacher Conners, physician rating

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Halperin,Gittelman, Katz, Struve (1986)	80 children considered hyperactive by teachers and parents or clinician; free of psychosis, neurological disorder, IQ > 80	Double-blind, four-week trial (two wks flexible dose MPD, two wks placebo) Teacher Conners, physician rating four wks after trial
Handen, Breaux, Gosling, Ploof Feldman (1990)	12 EMR and ADHD children, diagnosed through ADHD DSM-III-R criteria, Conners Parent and Teacher rating scales, IQ 50-74, Vineland mild to borderline MR	Double-blind, three-week trial (one wk. .3 mg MPD, one wk. .6 mg MPD, one wk. placebo) Teacher Conners, physician rating, rating four weeks after trial
Kimball (1986)	17 children "judged to be hyperactive by their physicians"	Double-blind 2-1/2 day trial Teacher Conners
Klorman, Brumaghim, Salzman, Strauss, Borgstedt, McBride, Loeb (1989)	63 children referred for treatment with stimulants, free of MR, psychosis, organic brain disorder, diagnosed as ADHD through rating scales and further divided into groups on basis of aggression scale	Double-blind, four-week trial (two wks. .3 mg MPD, two wks. placebo) Parent and Tacher Conners, Continuous Performance Test

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Loney, Comly, Simon (1975)	Two groups of 25 boys judged by clinicians as having good and poor parental management (using specified criteria)	All subjects previously placed on MPD Subjective rating
Loney, Langhorne, Paternite (1978)	135 boys recommended by psychiatrist for trial of stimulant medication "because their history and/or symptom picture suggested minimal brain dysfunction, " IQ > 70, not suffering from psychosis, sensory loss, epilepsy, cerebral palsy, or unequivocal brain damage	All subjects previously placed on MPD Subjective rating of chart progress notes
Loney, Prinz, Mishalow, Joad (1978)	84 non-retarded boys between age 6-12, living with both parents, placed on drug trial by judgment of senior psychiatrist	All patients previously placed on MPD Subjective rating of chart progress notes
McBride (1988)	53 boys and 17 girls diagnosed ADD through observation and report	Double-blind, four-week trial (two wks. .3 mg MPD, two wks. placebo) Parent and Teacher Conners, subjective report

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Payton, Burkhart, Hersen, Helsel (1989)	3 males with MR and ADDH; multiple diagnoses described	Three single subject designs with various schedules of placebo and MPD Movement, on-task behavior
Pelham, Walker, Sturges, Hoza (1989)	12 boys and 12 girls, matched for age and IQ, diagnosed as having ADD by senior author	Double-blind, approximately two-week trial (one wk. flexible dose MPD, one wk. placebo) Classroom academic and behavior measures, Teacher Conners, peer interactions
Pliszka (1989)	Clinical evaluation of DSM-III-R criteria, teacher rating, no psychotic or depressive disorder	Double-blind, four-week trial (two wks. placebo, one wk. .25 mg.-.40 mg. MPD, one wk. .45-.70 mg. MPD) Attentional behavior rating, memory test

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Porges, Walter, Korb, Sprague (1975)	Sixteen children diagnosed via Conners' ratings	Tested on last day of a 3-week period and during placebo Heart rate, reaction time
Rapoport, Abramson, Alexander, Lott (1971)	19 boys with persistent hyperactivity of at least several years duration, IQ > 85	Double-blind, four-week trial (two wks. flexible dose dextroamphetamine or chlorpromazine, two wks. placebo) Playroom observations, psychological tests
Rapoport, Quinn, Bradbard, Riddle, Brooks (1974)	76 children referred for persistent symptoms of hyperactivity, IQ > 80, absence of known neurological disorder	Double-blind, six-week trial (two wks. flexible dose MPD, two wks. flexible dose imipramine, two wks. placebo) Parent and Teacher Conners
Rie, Rie, Stewart, Ambuel (1974)	28 children diagnosed as ADHD by judgment of staff psychiatrist through cited criteria	Double-blind, 24-week trial (12 wks. flexible dose MPD, 12 wks. placebo)

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Rie, Rie, Stewart, Ambuel (1974) (cont.)		Activity level, achievement tests, IQ, parent and teacher rating
Satterfield, Cantwell, Lesser, Podosin (1972)	31 hyperkinetic males with no sensory defects, attending school, IQ > 80, diagnosed using specified criteria; and 21 normal controls	Double-blind, three-week trial (one wk. placebo, two wks. flexible dose MPD) Teacher Conners
Satterfield, Cantwell, Saul, Lesser, Podosin (1973)	57 boys with IQ > 80, normal vision and hearing, no evidence of gross neurological disease, diagnosed as hyperactive by behavioral criteria	Double-blind, three-week trial (one wk. placebo, two wks. flexible dose MPD) Teacher Conners
Schain, Reynard (1975)	82 males and 16 females with symptoms of "hyperactive behavior" significantly interfering with academic performance	16-week trial of flexible dose MPD; initial period of placebo Parent and Teacher Conners
Taylor, Schachar, Thorley, Wieselberg, Everitt, Rutter (1987)	38 boys with IQ > 65, "problems...severe enough to warrant psychiatric treatment...free of autistic features and overt neurological disease"	Double-blind, three-week trial (one wk. flexible dose MPD, one wk placebo, one wk break)

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Taylor, Schachar et al. (1987) (cont).		Teacher Conners, home and clinic behavior rating
Varley, Trupin (1982)	10 children with IQs ranging from 48 to 77, symptoms consistent with DSM-III diagnosis for ADD	Double-blind, three-week trial (one wk. .3 mg MPD, one wk. .6 mg MPD, one wk. pla[illegible])
		Parent and Teacher Conners
Voelker, Lachar, Gdowski (1983)	Medical records from 46 children with diagnosis of "hyper-kinetic reaction"	Retrospective rating of improvement after 2 months of MPD treatment
		Personality Inventory for Children
Weiss, Werry, Minde, Douglas, Sykes (1968)	40 children judged hyperactive by behavior reports and clinical activity, IQ>80	Double-blind, three to five week trial of either placebo, flexible dose chlorpromazine, or flexible dose dextroampheta-mine
		Parent rating, cognitive and motor function tests

Table 1 continued

Summary of Research on Prediction of Stimulant Response

Author(s)	Sample Composition	Drug Administration and Outcome Measure(s)
Zahn, Abate, Little, Wender (1975)	54 "MBD" children meeting specified criteria for hyperactivity, IQ > 80, absence of gross neurological disorder	One-time testing of children on and off medication Skin resistance, heart rate, reaction time

Other investigators, however, found no relationship between drug response and EEG abnormality (Rapoport, Quinn, Bradbard, Riddle, & Brooks, 1974; Weiss, Werry, Minde, Douglas, & Sykes, 1968) or found that abnormal EEGs predict poor drug responses (Schain & Reynard, 1975).

Halperin, Gittelman, Katz, and Struve (1986) note that the reasons for these conflicting results are likely due to methodological inconsistencies including ill-defined populations and the possibility of interaction with other variables such as age (as Barkley [1976] reports, younger children are more likely to demonstrate abnormal EEGs). In their study of a well-defined group of ADHD children, in which age and initial ratings of severity were controlled for, differences in medication response could not be predicted on the basis of EEG abnormalities or neurological soft signs.

Soft Signs

Many investigators have tried to relate the number of "soft" neurological signs (e.g., motor incoordination, gait or balance disorders, minor physical anomalies) to effective drug treatment outcome. Satterfield, Cantwell, Lesser, and Podosin (1972) found that hyperactive children with four or more soft signs had a more favorable response to drug treatment than those with fewer or no soft signs. Along with evidence of abnormally underaroused EEG's in

hyperactive children as noted above, Satterfield et al. (1972) concluded that children with evidence of organic brain damage responded more favorably to stimulant medication.

Similar results were reported by Conrad and Insel (1967), who noted that the presence of "organicity" (including the presence of soft signs and/or more overt neurological impairment) predicted favorable drug response better than "parental psychopathology" or other "emotional factors." Various subsequent researchers supported the hypothesis that evidence of neurologic soft signs effectively predicted good stimulant treatment outcome, including Epstein, Lasagna, Conners, and Rodriquez (1968), Ferguson and Trites (1980), and Taylor, Schachar, Thorley, Wieselberg, Everitt, and Rutter (1987).

However, other investigators have found no association between neurological soft signs or "organicity" and response to stimulant medication (Barkley & Jackson, 1977; Gualtieri & Hicks, 1985; Loney, Prinz, Mishalow, & Joad, 1978; McBride, 1988; and Schain & Reynard, 1975). As noted by Halperin et al. (1986),

> "It appears unlikely that a direct association exists between either EEG abnormalities or neurological soft signs and the behavioral disturbance of ADD-H. It is more likely that both the behavioral disturbance and these neurological

abnormalities are manifestations of other underlying neurophysiological disturbances" (p.824).

Sensory Integration

Another attempt to understand these "underlying neurophysiological disturbances" has come from the field of occupational therapy. Sensory integration therapy was developed by Ayres (1972) as a result of her theory stating that many types of childhood disabilities arise from immature integration of sensory input (most notably vestibular and proprioceptive). If sensory integrative dysfunction is present, a variety of output disabilities will necessarily arise. Within this framework, postrotary nystagmus (PRN) is utilized to test the integrity of a child's vestibular system, wherein a short duration of PRN indicates underaroused functioning. Children demonstrating underarousal are purported to respond well to sensory integrative occupational therapy techniques (Ayres, 1978). Sensory integration therapy includes techniques such as spinning children in hammocks, sliding, and swinging. These techniques are not widely accepted, but have long been utilized in the field of occupational therapy.

In an attempt to support the hypothesis that stimulant responders are underaroused (as noted above), Kimball (1986) tested 17 ADHD children previously judged to be responders

or non-responders to methylphenidate with sensory integrative measures. Children who were good responders demonstrated performance consistent with underarousal on the Southern California Postrotary Nystagmus Test (Ayres, 1975), while poor responders showed a reaction indicating overarousal (prolonged postrotary nystagmus, poorer equilibrium reactions). Although not replicated and relying on a small sample, these findings partially support the long-disputed hypothesis of neurological underarousal of good stimulant responders.

Despite over two decades of research, it is apparent that the relationship between neurological integrity and ADHD responsiveness has yet to be fully understood. Further, with research indicating that normal children and adults respond to stimulants in a way similar to ADHD children (thus refuting a "paradoxical" effect of stimulants on ADHD children) (Rapoport, Buchsbaum, Weingartner, Zahn, Ludlow, & Mikkelsen, 1980; Rapoport, Buchsbaum, Zahn, Weingartner, Ludlow, & Mikkelsen, 1978), most researchers have since turned to other avenues of research.

COGNITIVE MEASURES

Attention

In a review of 36 research studies published before 1976, Barkley reported that measures of Full Scale IQ,

academic ability, motor and graphomotor abilities, and personality/emotional measures did not effectively predict stimulant response. However, he did report that in a variety of studies, relatively poor performance on tasks of reaction time (Porges, Walter, Korb, & Sprague, 1975; Zahn, Abate, Little, & Wender, 1975), maze completion (Epstein, Lasagna, Conners, & Rodriguez, 1968), and number of toy changes in free play (Rapoport, Abramson, Alexander, & Lott, 1971) did have some predictive utility in discriminating good from poor drug responders. In his unpublished doctoral dissertation (cited in Barkley, 1976), Barkley directly tested this hypothesis by administering a wide variety of tests of activity level and attention to a group of ADHD children. In this sample, Barkley reported that the higher the child's activity level and inattention (before administration of stimulant medication), the greater the improvement displayed by that child in activity level. He concluded, "...those psychological measures associated with attention span have been found to be the most sensitive predictors of differential drug response in hyperkinetic children" (Barkley, 1976).

Since 1976, the majority of attempts at further validation have been supportive, with most investigators also finding that higher levels of inattentive and restless behavior or impaired performance on measures of attention predicted good response to medication (Ferguson & Trites,

1980; Loney, Prinz, Mishalow, & Joad, 1978; Taylor et al., 1987). One study (Rie, Rie, Stewart, & Ambuel, 1976) partially validated this result, with an inconsistent relationship reported among pre-drug trial measures of activity level and parental rating scales.

Measures of initial attention and activity level therefore appear to be relatively consistently predictive of stimulant drug response. As Loney et al. (1978) note, however, it is unclear whether,

> "...what improvement he [a "responding" child with ADHD] does show is merely more discernibly different from his previous high rate of hyperactive behavior than is an equal improvement in a child who was less severely hyperactive...or that high hyperactivity scores are simply more likely to display a statistically artifactual regression to the mean..." (p. 1490).

IQ

The WISC-R has also been used in an attempt to discriminate between responders and non-responders. Barkley notes that before his review of 1976, only one study (Rie, Rie, Stewart, & Ambuel, 1976) reported effective prediction of improvement using WISC Full Scale and Performance IQ's. Other studies (Buschbaum & Wender, 1973; Hoffman, Engelhardt, Margolis, Polizos, Waizer, & Rosenfeld, 1974;

Knights & Hinton, 1969; Rapoport, Abramson, Alexander, Lott, 1971; Satterfield et al., 1972; Weiss et al., 1968; Werry & Sprague, 1974; Zahn et al., 1975) found the Full Scale WISC or WISC-R ineffective for prediction of medication response in children with average IQs. More recent investigations utilizing the WISC-R (Ferguson & Trites, 1980; McBride, 1988) are reported below.

Other research has examined the relationship between children with ADHD and subaverage IQs and stimulant response. Only a few medication studies of this type have been reported (Aman, Marks, Turbott, Wilsher, & Merry, 1991; Handen, Breaux, Gosling, Ploof, & Feldman, 1990; Payton, Burkhart, Hersen & Helsel, 1988; Varley & Trupin, 1982). with three out of four studies reporting positive drug effects (Handen et al., 1990; Payton et al., 1989; Schell et al., 1986; and Varley & Trupin, 1982) and Aman et al. (1991) indicating an equivocal response to medication. Methodological inconsistencies again must be addressed in interpreting these results, since small populations, diverse population definitions and different outcome measures were used.

A subgroup of language delayed hyperactive children has been reported by Beitchman, Tuckett, and Batth (1987); it is possible that these children also respond distinctly to stimulant medication. As of this date, only one researcher has separated the WISC-R into Verbal and Performance IQs

(McBride, 1988); in this study, the Verbal IQ and the Full Scale IQ of nonresponders were lower than that of responders. These results have not been replicated.

No research has been published to date examining the predictive utility of specific WISC-R subtests, particularly those thought to measure attentional capacity (Digit Span, Coding, and Arithmetic).

Overall, initial measures of attention span appear to be promising for the prediction of medication response. More global measures of cognitive functioning (e.g., intellectual quotient) have not proven effective in discriminating good from poor drug responders. It is possible that subtest analysis of the WISC-R would be effective for discrimination of responders and non-responders, but further research is needed in this area.

DEMOGRAPHIC PREDICTORS

A few studies have examined the relationship between drug response and demographic or sociological variables such as sex, age, race, and socioeconomic status (SES) in addition to an assortment of other variables.

In the first systematic investigation of this type, Loney, Prinz, Mishalow, and Joad (1978) reported that age at referral accounted for a significant amount of variance in their outcome measure (blind rating of chart information),

with older children responding better to stimulants than younger children. In their multivariate design, Loney et al. also found that perinatal complications (as determined through chart review) and a "hyperactivity factor" (a measure of symptom severity at referral, evaluated through chart review of distractibility, impulsivity, and related behaviors) accounted for a lesser (but statistically significant) amount of variance in stimulant responsivity. Parenting style, neurological status, SES, and aggression were not predictive of response. These results led to further research regarding relative weights of predictive variables, but as Loney et al. (1978) attest,

> "The data are less objective, focused, and systematic than one would wish, and they are filtered through the multiple perspectives of parents, teachers, treating physicians, and raters. For these reasons, one might consider the present results as generating hypotheses about predictors of response to methylphenidate rather than as identifying predictors" (p. 1489).

Ferguson and Trites (1980) also used demographic and other variables but collected data prospectively in their study of 79 ADHD boys. They also found age to be predictive of stimulant response but in the opposite direction as Loney et al. (1978), with younger children responding best. They

found that responders had more minor physical anomalies (again inconsistent with Loney et al.), had lower IQ scores than nonresponders, and were less attentive (as suggested by Barkley, 1976) than non-responders. They report that those children considered brain damaged (on the basis of neuropsychological assessment only) had a higher rate of response than those without evidence of brain dysfunction. Unfortunately, Ferguson et al. (1980) utilized only chi-square analyses in reporting their data. Therefore, information regarding relative predictive weights of variables was not available, as would be the case if a multivariate design were employed.

Taylor et al. (1987) also examined the relationship of demographic and other variables and stimulant response in 38 boys referred for ADHD. They found that young age, initial ratings of hyperactivity (restless/inattentive opposed to impulsive/non-compliant), motor incoordination, and the absence of symptoms of emotional disorder effectively predicted good drug response. History of family psychopathology, perinatal complications, and SES were not predictive in this sample. Taylor et al. called for future work to validate their results, especially given the relatively small number of subjects utilized.

Since the prevalence of boys with ADHD (9%) is significantly larger than that of girls (2%) (Barkley, 1981) and they often present with differing symptom patterns

(Berry, Shaywitz & Shaywitz, 1985; deHaas & Young, 1984), it is reasonable to hypothesize that their response to medication might also differ. However, the aforementioned studies utilized only boys as subjects, and gender was not evaluated until McBride (1988). McBride found that distractibility in the office setting, and gender (male) predicted good response, while neurological findings, age, and EEG results did not. This lower response rate among girls is intriguing, but was not replicated by Pelham, Walker, Sturges, & Hoza (1989), who reported that methylphenidate was equally effective in their sample of 12 boys and 12 girls for improving attentional behaviors.

In sum, these studies have not found SES or race to be effective predictor variables. The majority of studies have found various indications of neurological dysfunction and attentional deficit predictive of good stimulant response, but results are not consistent. The relationship of gender to stimulant responsiveness is also currently unclear.

A variable which has consistently been found to predict treatment response is age, but results have been in contradictory directions. Several researchers have demonstrated the effectiveness of stimulants in the adolescent ADHD population (Klorman, Coons, & Borgstedt, 1987; Lerer & Lerer, 1977; MacKay, Beck, & Taylor, 1973), and the differential effect of stimulants as a function of

age has also received limited attention. Ferguson and Trites (1980) have found that younger children (at time of referral) tend to respond better to stimulant medication, and Safer and Krager (1989) also report that younger children respond best to medication. Loney et al. (1978), however, reported that older children responded best in their sample, as did Halliday, Gnauck, Rosenthal, McKibben, and Callaway (1980). Other investigators have reported no significant differences in drug responsiveness on the basis of age (McBride, 1988).

PSYCHOPATHOLOGICAL PREDICTORS

Parenting/Familial Variables: Some researchers have reported a better response to medication in those children with "good" parent-child relationships and/or the absence of parental pathology. Loney, Comly, and Simon (1975) and Conrad and Insel (1967) reported that hyperactive children rated as having better mother-child relationships had a better rate of drug responsiveness than those with poor relationships. Conrad and Insel (1967) also noted that a group of children living with parents rated as "grossly deviant" or "socially incompetent" had fewer responders than a group living without such a parent. Barkley and Cunningham (1979) also report that the better the mother-child relationship, the greater the response to medication. They postulate that mothers who are more appreciative and

rewarding of positive changes initially produced by medication may produce further gains. However, Loney et al. (1978), Taylor et al. (1987), and Weiss, Werry, Minde, Douglas, and Sykes (1968) failed to find a positive relationship between parent-child relationships or marital stability and stimulant drug response. Again, differences in measures, sample composition, and treatment schedules must be considered in the evaluation of these results (see Table 1).

Comorbidity: Due to the comorbidity of ADHD with other psychiatric diagnoses, subgrouping children with ADHD on the basis of coexisting disorders has been suggested (Biederman, et al., 1991). The differences in these children's response to medication has been previously examined. Conrad and Insel (1967) found that a group of hyperactive children with "emotional pathology" but without neurological soft signs had significantly fewer good drug responders than a group of children with neurological soft signs and without emotional pathology. Zahn, Abate, Little, and Wender (1975) and Taylor et al. (1987) also reported that higher levels of "emotional problems" were associated with a poorer response to stimulants.

Although several coexisting psychiatric diagnoses may exist, Anderson, Williams, McGee, and Silva (1987) reported that 47% of children with ADD had a coexisting conduct or oppositional defiant disorder, and approximately 26% of

children with ADD had a coexisting anxiety or phobic disorder. Due to this marked overlap in diagnoses, recent studies have examined the relationships among ADHD, Conduct disorder and Overanxious disorder.

1) Conduct/Oppositional defiant disorder: The presence of Conduct disorder or aggression in addition to ADHD has been studied by a limited number of investigators. Loney, Langhorne, and Paternite (1978) reported that boys with fewer aggressive symptoms and more hyperactive symptoms tended to respond better to stimulant medication. Klorman, Brumaghim, Salzman, Strauss, Borgstedt, McBride, and Loeb (1989) reported no differences in stimulant response between ADHD children with and without non-compliant features. These results were partially supported by Barkley, McMurray, Edelbrock, and Robbins (1989) and Loney et al. (1978), who found that "aggressives" and "non-aggressives" responded similarly in their response to medication. These studies are difficult to evaluate, however, given differences in measures and inadequate information to compare non-compliance with aggression.

2) Overanxious disorder: Rapoport et al. (1974) reported that children judged as most inhibited and anxious responded best to stimulant medication, while those considered most aggressive/conduct disordered deteriorated when placed on stimulants. Voelker, Lachar, and Gdowski (1983) and Pliszka (1989), however, found that those ADHD

children with comorbid anxiety had a significantly poorer response to stimulant medication than those without anxiety.

OTHER VARIABLES

The issue of family structure type has not been previously explored with regard to medication response. The potential for adverse effects of divorce and single-parent status on child adjustment have been previously reported (Egeland & Farber, 1984; Kellam, Ensminger, & Turner, 1977), particularly when the child is "...difficult to teach (e.g., hyperactive/emotional/dependent)" (Pianta, Sroufe, & Egeland, 1989). In addition, the presence of an involved father in the home has been found by Earls, Beardslee, & Garrison (1987) as more important than child-related variables in predicting child competence. Kellam et al. (1977) report that "mother alone" families entailed the highest risk in terms of social maladaptation and psychological well-being of the child, while the presence of a second adult appeared to have certain ameliorative functions. Although it is evident that several mediating variables (children's temperament and developmental status, family relations, and extrafamilial factors) are unquestionably important in the overall impact of changes in family structure (Hetherington, 1989; Hetherington, Cox, & Cox, 1986; Hetherington, Hagan, & Anderson, 1989), it would be interesting to explore family structure in a preliminary

way with respect to stimulant response.

An additional variable that has yet to be evaluated is that of adoptive status. At least one study (Verhulst, Althous, & Verluis-DenBieman, 1990) has indicated that adopted boys between the ages of 12 and 15 years are at significantly greater risk for ADHD than non-adopted boys. It is possible that adopted children differ somehow from non-adopted children in their response to medication: additional factors may be associated with adoption that could variably affect a child's medication response. This variable has not been researched.

Chosen interactions among above-noted variables are also of interest. Previous research has suggested that ADHD girls do not differ diagnostically from Conduct Disordered girls (Szatmari, Boyle, & Offord, 1989). In addition, boys have been found to respond more favorably to stimulant medications (McBride, 1988). The interaction between sex and diagnosis in regard to stimulant response would therefore be interesting to evaluate. Interactions between age and gender are also of interest, given conflicting results as noted above. Finally, evidence suggests that SES may play a role in mediating the effect of family constellation (Hetherington, 1989). While family structure type may not be significant in isolation, its relationship with regard to SES is worth evaluation.

IV. SUMMARY

As indicated, research studies to date have revealed inconsistent results regarding the isolation of effective variables to identify those children who will respond positively to stimulant drug medication. Attempts at identifying neurophysiological and neuroanatomical predictor variables have generally proven inconsistent, although there is some evidence to suggest that the presence of "organicity" may predict a better medication response. In addition, there is some evidence that the more severe the attentional difficulty, the better the medication response. Some demographic (age and sex) and familial (parental psychopathology) variables have also shown promise as effective predictor variables. Finally, recent research indicates that the presence of other diagnoses in addition to ADHD may variably affect a child's response to medication.

It is important to note that wide differences in research design and population composition exist. In addition, widely differing methods for the measurement of outcome have been utilized. Until a body of research is described utilizing similar populations and measures, research with regard to prediction of stimulant response will be difficult to evaluate.

Thus, although the prediction of medication response is an important question, it remains largely unanswered. Many

predictor variables have been advanced, but relationships between predictor and criterion variables have generally been of limited value clinically (although statistically significant) in size. In addition, few multivariate investigations have been reported which take into account these variables' relative predictive weights.

The present study addresses weaknesses in the existing literature by investigating the multivariate relationship between several predictor variables and medication response in a large, clinic-referred sample. This study also assesses longer-term outcome: an important, but previously neglected, variable.

PART B

METHOD

I. SUBJECTS

The 336 children whose medical records were included in this study were 58 girls and 278 boys, aged 3 to 16 years, with a mean age of 8.6 years. Permission for use of medical records for research purposes had been obtained upon initial treatment. Subjects had been referred to the outpatient psychiatric clinic in a regional children's hospital between 1985 and 1990. Referrals were made by parents, teachers, physicians, and/or mental health workers for psychiatric assessment of disruptive, inattentive, or overactive behavior, or for consultation regarding stimulant medication treatment.

Children evaluated before 1987 met criteria for Attention Deficit Disorder with or without Hyperactivity (American Psychiatric Association, 1980). Children evaluated after 1987 met diagnostic criteria for Attention-Deficit Hyperactivity Disorder (American Psychiatric Association, 1987), as determined by the treating clinician. In 180 cases, this clinician was a nurse practitioner under the supervision of a sole child psychiatrist. In 156 cases, the diagnosis was made by one of three staff child psychiatrists. Due to the retrospective nature of this design, interrater reliability could not be empirically assessed. Base diagnostic rates in this clinic are not known.

The presence of concurrent neurological conditions and/or measured IQs of less than 65 were noted, but no child

was excluded from the study on those grounds (four children had measured IQs of less than 65; 89% had Full Scale IQs between 80 and 120). All children were considered free of contraindications to stimulant medication treatment (e.g., tics or cardiovascular disease).

II. TREATMENT

All children included in this study had completed a three week, double-blind trial of methylphenidate and placebo at home under the supervision of a staff psychiatrist. This three week trial consisted of administration of three conditions assigned to each child in random order: 1) one week of placebo, 2) one week of 0.5 mg/kg/day of methylphenidate, and 3) one week of 1.0 mg/kg/day of methylphenidate. The medication was prepared by the hospital pharmacy in identical capsules and was administered twice daily, at 8 a.m. and at noon. Due to the retrospective nature of this design, compliance with the medication trial could not be empirically assessed.

III. MEASURES

Predictor Variables:

Demographic/Familial Variables:

- Age at initiation of drug trial; this variable has been significant for prediction in previous studies but in varying directions.

- Gender; differing response rates for boys and girls have been reported but not yet replicated.

- Socioeconomic Status (SES), based on data regarding parental education and occupation (Hollingshead, 1975).

- Family Structure Type (mother alone vs. other). Although several mediating variables are unquestionably important, a preliminary exploration of the relationship between family structure type and medication response in this group of ADHD children was carried out.

- Adoptive status (natural child vs. adopted child).

- Neurological status (presence of neurological diagnosis, e.g. seizure disorder, vs. absence of diagnosis).

Child Behavior Checklist (CBCL) (Achenbach & Edelbrock, 1983):

- CBCLs were completed by 168 parents and 123 teachers before initiation of the drug trial. T-scores on "internalizing" and "externalizing" factors of the CBCL (as rated by parents and teachers separately) were recorded. These groupings have been repeatedly identified in factor analyses of the CBCL, and are thought to reflect "...a distinction between fearful, inhibited, overcontrolled behavior, and aggressive, antisocial, and undercontrolled behavior" (Achenbach & Edelbrock, 1983). This measure was

theorized to parallel (but not explain) the diagnoses of overanxious and conduct disorder, as noted above.

The presence of a T-score exceeding 70 on one or more subscale(s) of the CBCL was also recorded.

Wechsler Intelligence Quotient (IQ) (Wechsler, 1974):

- Full Scale WISC-R IQ values were obtained previous to the drug trial through a variety of Western Washington State school districts for 155 children.

- A "Freedom From Distractibility" measure was calculated by subtracting the mean total of the Arithmetic, Digit Span, and Coding subtests from the mean remainder of WISC-R subtest scores (see Kaufman, 1974).

Criterion Variables:

1) Conners' Teacher (Conners, 1969) and Parent (Conners, 1973) Rating Scales were collected daily for the determination of medication response. Mean ratings for each week (placebo, 0.5 mg methylphenidate, 1.0 mg methylphenidate) were calculated. An overall response rating was then calculated by subtracting the mean placebo

rating from the lowest mean methylphenidate rating. Mean ratings across parents and teachers, as well as separate parent and teacher ratings, were recorded.

For 147 parents and 163 teachers, numerical Conners ratings were not available. Instead, a subjective response was noted by the clinician (e.g., "Both parent and teacher stated that Johnny's behavior was best during week 1, worst during week 2, and somewhere in between for week 3"). For these cases, responses were recorded dichotomously; if the subject responded better than placebo on either week during which methylphenidate was administered, he/she was considered a "yes" responder. If the child's behavior was considered better while on placebo than during either drug week, he/she was considered a "no" responder. If no difference was reported between placebo and either methylphenidate week, the subject was considered a "no" responder.

For those children for whom numerical Conners ratings were available, scores were also coded for compatibility with those above: children who performed better during either methylphenidate week were considered "yes" responders, and those who performed better during the placebo week were considered "no" responders.

Numerical ratings were additionally coded to identify those who responded with a difference in Conners' rating of equal to or greater than 6.0 points (approximately two

standard deviations) on either methylphenidate week compared to placebo. These responders were considered "strong" responders.

2) Those children who continued to take methylphenidate subsequent to the double-blind trial (regardless of the results on the trial) were labelled "continued".

3) Additional information regarding longer-term outcome was assessed in a subset of children through a follow-up telephone interview with their primary caretaker. The caretakers of children treated from January 1, 1988 - December 31, 1989 were contacted through an initial mailing (see Appendix A) inviting voluntary participation in the study (N=90). Thirty-three (36.67%) caretakers responded to this mailing and were subsequently contacted via telephone.

For those children who were still taking stimulant medication, information regarding aggressive/inattentive behavior was rated by the primary caretaker. An overall functional status rating was also collected (see Appendix B).

IV. MISSING VALUES

Values were missing for a variety of predictor variables (most often CBCL, IQ, or SES) in a number of cases. Of the 336 medical records reviewed, 300 were missing information for one or more predictor variables.

Refer to Table 2 for information regarding the extent of missing data for individual predictor variables. These data were missing for a variety of reasons which are not considered unique to the missing samples (i.e., missing intake forms, clinician variability, inconsistent parental and teacher follow-through, etc.).

One possible exception is in the case of WISC-R IQ (Wechsler, 1974). Since IQ tests are usually given only to those children who are identified as a "Focus of Concern" by school personnel or parents, these children could feasibly be more overtly symptomatic than children who did not receive IQ tests. For this reason, children with and without IQ scores were compared on their CBCL Externalizing Mean Scores in order to determine whether significant differences emerged. (Mean CBCL-E scores were as follows: Missing IQ = 68.3, With IQ = 68.2.) A t-test revealed no group differences (t = .32, p = .750) on this measure.

Mean values for existing data were therefore entered in place of missing values for the following analyses, unless otherwise indicated.

PART C

HYPOTHESES AND PLANNED ANALYSES

I. PRIMARY HYPOTHESES

a) For those cases in which a numerical Conners rating is available, a step-wise multiple regression analysis will be carried out to test the hypothesis that neurological status, WISC-R Freedom From Distractibility, age, and sex will be significantly related to the primary criterion variable (mean Conners rating), while family constellation type, SES, and CBCL measures will not account for a significant amount of variance in the outcome measure.

b) A discriminant function analysis will be carried out on all cases (N = 336) to determine which (if any) predictor variables can successfully discriminate between responding and non-responding groups. Again, it is hypothesized that neurological status, WISC-R Freedom From Distractibility, age, and sex will successfully discriminate between the two groups.

II. SECONDARY ANALYSES

Several additional important questions regarding the interrelationships among these data will be addressed through a series of secondary analyses, as follows:

a) Some evidence has indicated that hyperactive behaviors are situationally specific (Landman & McCrindle, 1986), and that the rating source (e.g., parent vs. teacher) must be taken into account in ADHD research (Johnson &

Prinz, 1976; Langhorne, Loney, Paternite & Bechtoldt, 1976). Other researchers, however (e.g., Pinto & Tryon, 1990), have presented data indicating that hyperactive behaviors are likely to be pervasive in nature. To evaluate these effects in the context of the present study, multiple regression analyses will be carried out on parents' and teachers' ratings separately to determine if differing results emerge. It is hypothesized that results will remain stable, regardless of rater source. It is also hypothesized that correlations will be higher when parent and teacher data are evaluated separately.

b) For the groups in I.b above, even those subjects who responded only minimally were classified as "responders." It is therefore important to separately evaluate those subjects who demonstrated a more definite, "strong" positive response to methylphenidate, in order to determine whether differing results emerge. It is hypothesized that significant predictor variables (as identified in I.b above) will remain stable, but that these variables will account for more variance in mean Conners rating of the "strong" responders.

c) The mean parent and teacher Conners rating will be correlated with the "continue" measure. This post-hoc analysis tests whether results of the double-blind drug trial determined if the child was placed on medication. It

is hypothesized that this correlation will be very high and significant at $p<.001$.

d) The interaction between sex and externalizing symptomatology on the CBCL will be evaluated in an attempt to support the hypothesis that boys without the presence of aggressive/non-compliant symptoms will respond best to stimulant medications. This analysis is only preliminary in nature, since high CBCL-E scores are not necessarily indicative of conduct disorder.

e) Contradictory findings have been reported with regard to both age and sex. In order to more fully investigate these variables, interactions of age and sex will be tested in order to determine whether any significant relationships emerge.

f) Although family constellation type will be interesting to explore, it is hypothesized that this variable will not be significant in isolation. This variable will be evaluated with regard to its relationship with SES to test the hypothesis that as SES increases, children living with their mothers alone will tend to respond better to medication.

III. FOLLOW-UP DATA ANALYSES

a) A discriminant function analysis will be repeated for those subjects in which follow-up data is available in order to determine whether differing results emerge. It is

hypothesized that predictor variables will not change, but that prediction will be more powerful when follow-up data is included as part of the outcome measure.

b) It is hypothesized that subjects who were classified as "strong" responders on initial drug trial are more likely to remain on medication at follow-up than those subjects who responded more equivocally. This hypothesis will be tested through the use of a chi-square analysis.

c) It is hypothesized that those children who experienced significant side effects to methylphenidate will be less likely to have continued on medication at follow-up.

PART D

RESULTS

RESULTS

Results will be presented as outlined below:

I. POPULATION MEANS

II. CORRELATIONS

III. MULTIPLE REGRESSION ANALYSES: For these analyses, only those subjects for whom numerical Parent (N = 189) and Teacher (N = 173) Conners ratings were available were utilized. Split-half validation (Table 4) and Parent vs. Teacher (Table 5) predictions are reported. Cases with complete data are analyzed in Table 6.

IV. DISCRIMINANT FUNCTION ANALYSES: For these analyses (N = 336), criterion was determined through either numerical Conners ratings or through subjective response, resulting in a dichotomous measure. An overall discriminant function analysis and splif-half validation are reported in Table 7. Parent vs. Teacher ratings (Table 8) and complete data analyses (Table 9) follow.

V. ANALYSES OF "STRONG" RESPONDERS

VI. ANALYSES OF CONTINUATION ON MEDICATION

VII. INTERACTIONS

VIII. FOLLOW-UP DATA ANALYSES

I. POPULATION MEANS

Table 1 presents frequencies and means (where applicable) for all variables.

The following information is notable:

1. The ratio of boys to girls in this sample (9:1.88) is in accordance with Barkley's (1991) report of a 9:2 ratio of hyperactive boys to girls in the general population.

2. Eleven children presented with a neurological diagnosis. Six children were diagnosed with seizure disorder, one child had Klinefelter syndrome, one child had fetal alcohol syndrome and mild mental retardation, one child had severe mental retardation, one child had muscular dystrophy, and one child was noted to be "neurologically impaired" with no further explanation.

3. As noted, mothers' occupational status was rated somewhat higher than fathers' in this sample. This is due to Hollingshead's occupational rating system, wherein "clerical" jobs (traditionally held by more females, e.g. secretary, receptionist) are rated higher in status than "skilled manual labor" jobs (traditionally held by more males, e.g. mechanic, carpenter). If income were also taken into account, it is likely that the mothers' occupational status would be considerably lower than the fathers'.

Table 2

Descriptive Statistics

Sex	N	%
Male	278	82.7
Female	58	17.3
TOTAL	336	100.0

Age	$\bar{X}$	S.D.	Min.	Max.
	8.57	2.68	3.3	16.7

Neurological Diagnosis	N	%
Absent	277	82.4
Present	11	3.3
Missing	48	14.3
TOTAL	336	100.0

Adoptive Status	N	%
Adopted	21	6.3
Not Adopted	285	84.8
Missing	30	8.9
TOTAL	336	100.0

Table continues

Table 2 continued

Descriptive Statistics

Family Structure Type	N	%
Mother Alone	67	19.9
Mother and Biological Father	176	52.4
Mother and Other Adult Partner	41	12.2
Father Alone	2	.6
Other	26	7.7
Missing	24	7.1
TOTAL	336	100.0

Occupation

Father	Value	N	%
Menial Service/Farm Worker	1	7	2.1
Unskilled Labor	2	5	1.5
Semiskilled Labor	3	38	11.3
Skilled Manual Labor	4	52	15.5
Clerical	5	33	9.8
Semiprofessional	6	22	6.5
Manager	7	24	7.1
Administrator	8	22	6.5
Higher Executive/Professional	9	11	3.3
Home or None	10	7	2.1
Missing	.	115	34.2
TOTAL		336	100.0

$\bar{X}$ = 5.20, Standard Deviation = 2.15

Table continues

Table 2 continued

Descriptive Statistics

Occupation

Mother	Value	N	%
Menial Service/Farm Worker	1	8	2.4
Unskilled Labor	2	15	4.5
Semiskilled Labor	3	21	6.3
Skilled Manual Labor	4	29	8.6
Clerical	5	51	15.2
Semiprofessional	6	34	10.1
Manager	7	7	2.1
Administrator	8	14	4.2
Higher Executive/Professional	9	5	1.5
Home or None	10	80	23.8
Missing	.	72	21.4
TOTAL		336	100.0

$\bar{X}$ = 6.37, Standard Deviation = 2.86

Education

Father	Value	N	%
Junior High	2	2	.6
Partial High School	3	14	4.2
High School Graduate	4	79	23.5
Partial College	5	74	22.0
College Graduate	6	52	15.5
Graduate Degree	7	9	2.7
Missing	.	106	31.5
TOTAL		336	100.0

$\bar{X}$ = 4.81, Standard Deviation = 1.01

Table continues

Table 2 continued

Descriptive Statistics

Education

Mother	Value	N	%
Junior High	2	1	.3
Partial High School	3	19	5.7
High School Graduate	4	108	32.1
Partial College	5	93	27.7
College Graduate	6	36	10.7
Graduate Degree	7	8	2.4
Missing	.	71	21.1
TOTAL		336	100.0

$\bar{X}$ = 4.63, Standard Deviation = .92

Socioeconomic Status	$\bar{X}$	S.D.	Min.	Max.
	39.68	9.91	11.0	66.0

WISC-R IQ

	$\bar{X}$	S.D.
Verbal IQ	99.4	17.6
Performance IQ	100.2	19.0
Full Scale IQ	99.4	17.7
Information	10.1	3.4
Similarities	10.9	3.8
Arithmetic	8.5	2.9
Vocabulary	9.9	3.6
Comprehension	10.1	3.0
Digit Span	8.4	3.3

Table continues

Table 2 continued

Descriptive Statistics

WISC-R IQ cont.		
Picture Completion	10.2	2.9
Picture Arrangement	10.3	3.6
Block Design	10.2	3.8
Object Assembly	10.5	3.6
Coding	8.6	3.5
N = 155		

Child Behavior Checklist

Parent Scale
(N=168)

	$\bar{X}$	S.D.
Internalizing T-Score	65.3	8.7
Externalizing T-Score	69.5	7.9

Spike (Any subscale over T=70)

Yes	136
No	32
...	168
TOTAL	336

Teacher Scale
(N=123)

	$\bar{X}$	S.D.
Internalizing T-Score	61.5	8.8
Externalizing T-Score	67.0	8.4

Spike (Any subscale over T=70)

Yes	71
No	52
...	213
TOTAL	336

Table continues

Table 2 continued

Descriptive Statistics

Continuation on Medication after Drug Trial	N	%
Yes	282	83.9
No	54	16.1
TOTAL	336	100.0

Conners Rating Scale			
Numerical Difference Score		$\bar{X}$	S.D.
	Parent (N=189)	5.91	6.05
	Teacher (N=173)	6.92	6.10
Dichotomous Rating			
		Freq	%
	Parent		
	Yes	271	80.7
	No	62	18.5
	...	3	.9
	TOTAL	336	100.0
	Teacher		
	Yes	235	69.9
	No	45	13.4
	...	56	16.7
	TOTAL	336	100.0

II. CORRELATIONS

Refer to Table 3 for correlations among predictor and criterion variables.

III. MULTIPLE REGRESSION ANALYSES

1.a. Table 4 presents results of a stepwise multiple regression analysis of age, sex, neurological diagnosis, adoptive status, family structure type, socioeconomic status, Full Scale IQ, Freedom From Distractibility, Mean Parent and Teacher CBCL Internalizing T-Score, Mean Parent and Teacher CBCL Externalizing T-Score, and Mean Parent and Teacher CBCL Spike on Mean Conners Rating Scale.

Results indicate that the Freedom From Distractibility measure accounts for a small, but significant, amount of variance in the outcome measure. After this variance is accounted for, the CBCL Externalizing T-Score then accounts for a small, but significant amount of variance. The remaining predictor variables were not significant and were not entered into prediction equations. This analysis indicates that those children who present with more inattentive and hyperactive behaviors, as measured by the WISC-R and the CBCL, are more likely to respond positively to stimulant medication.

1.b. For purposes of validation, the above regression was repeated after randomized split-half sampling. Table 4 also presents results of this analysis.

Table 3

Correlations of Predictor and Criterion Variables (N = 336)

	Sex	Age	NDX	Adp	Fam
Sex	1.000	-.042	.092	.073	.057
Age	-.042	1.000	.066	.049	.049
NDX	.092	.066	1.000	.022	-.045
Adp	.073	.049	.022	1.000	.165*
Fam	.057	.045	-.045	.165*	1.000
SES	.017	.061	-.068	.011	.003
FS	-.073	-.055	-.101	-.036	-.017
FFD	-.021	.007	-.013	.024	-.055
MCI	.075	.105	-.043	-.026	-.039
MCE	.016	-.006	-.088	-.011	-.065
MSP	.079	.074	.017	.036	.027
PCI	.055	.055	.002	-.059	-.065
PCE	.028	-.005	-.096	-.009	-.053
PSP	.062	.018	-.008	.004	-.020
TCI	.062	.112	-.074	.025	.009
TCE	-.004	-.005	-.040	-.008	-.049
TSP	.051	.086	.031	.046	.056
PCN	-.085	.011	-.089	.014	.014
TCN	.005	-.095	-.182**	.057	.007

Table continues

Table 3 continued

Correlations of Predictor and Criterion Variables (N = 336)

	SES	FS	FFD	MCI	MCE
Sex	.017	-.073	-.021	.075	.016
Age	.061	-.055	.007	.105	-.006
NDX	-.068	-.101	-.013	-.043	-.088
Adp	.011	-.036	.024	-.026	-.011
Fam	.003	-.017	-.055	-.039	-.065
SES	1.000	.134*	.007	.050	-.075
FS	.134*	1.000	.183**	-.010	-.013
FFD	.007	.183**	1.000	-.079	.019
MCI	.050	-.010	-.079	1.000	.488**
MCE	-.075	-.013	.019	.488**	1.000
MSP	-.068	-.085	-.026	357**	.508**
PCI	.044	.011	-.014	.812**	.459**
PCE	-.012	-.019	.033	.460**	.809**
PSP	.014	-.079	-.004	.438**	.419**
TCI	.034	-.030	-.115	.738**	.288**
TCE	-.111	.000	-.004	.303**	.767**
TSP	-.107	-.044	-.032	.366**	.315**
PCN	.028	-.046	.127*	-.057	.040
TCN	.014	-.040	.055	.077	.147*

Table continues

Table 3 continued

Correlations of Predictor and Criterion Variables (N = 336)

	MSP	PCI	PCE	PSP	TCI
Sex	.079	.055	.028	.062	.062
Age	.074	.055	-.005	.018	.112
NDX	.017	.002	-.096	-.008	-.074
Adp	.036	-.059	-.009	.004	.025
Fam	.027	-.065	-.053	-.020	.009
SES	-.068	.044	-.012	.014	.034
FS	-.085	.011	-.019	-.079	-.030
FFD	-.026	-.014	.033	-.004	-.115
MCI	.557**	.812**	.460**	.438**	.738**
MCE	.508**	.459**	.809**	.419**	.288**
MSP	1.000	.432**	.381**	.695**	.435**
PCI	.432**	1.000	.609**	.586**	.207**
PCE	.381**	.609**	1.000	.547**	.068
PSP	.695**	.586**	.547**	1.000	.058
TCI	.435**	.207**	.068	.058	1.000
TCE	.421**	.093	.243**	.094	.400**
TSP	.742**	.055	.019	.034	.550**
PCN	-.027	.002	.079	.023	-.098
TCN	.085	.059	.078	.028	.059

Table continues

Table 3 continued

Correlations of Predictor and Criterion Variables (N = 336)

	TCE	TSP	PCN	TCN
Sex	-.004	.051	-.085	.005
Age	-.005	.086	.011	-.095
NDX	-.040	.031	-.089	-.182**
Adp	-.008	.046	.014	.057
Fam	-.049	.056	.014	.007
SES	-.110	-.107	.028	.014
FS	.000	-.044	-.046	-.039
FFD	-.004	-.032	.127*	.055
MCI	.303**	.366**	-.057	.077
MCE	.767**	.315**	.040	.147*
MSP	.421**	.742**	-.027	.085
PCI	.093	.055	.002	.059
PCE	.243**	.019	.079	.078
PSP	.094	.034	.023	.028
TCI	.400**	.550**	-.098	.059
TCE	1.000	.498**	-.021	.157*
TSP	.498**	1.000	-.058	.093
PCN	-.021	-.058	1.000	.338*
TCN	.157*	.093	.338**	1.000

*p<.01 **p<.001

Key: NDX = Neurological Diagnosis
Adp = Adoptive Status
Fam = Family Structure Type
SES = Socioeconomic Status
FS = Full Scale WISC-R IQ
FFD = Freedom From Distractibility Factor
MCI = Mean CBCL Internalizing T-Score
MCE = Mean CBCL Externalizing T-Score
MSP = Mean CBCL Spike
PCI = Parent CBCL Internalizing T-Score
PCE = Parent CBCL Externalizing T-Score
PSP = Parent CBCL Spike
TCI = Teacher CBCL Internalizing T-Score
TCE = Teacher CBCL Externalizing T-Score
TSP = Teacher CBCL Spike
PCN = Parent Conners Score (dichotomous)
TCN = Teacher Conners Score (dichotomous)

Table 4

Prediction of Parent and Teacher Conners (N = 168)

Variables Entered Into The Equation:

1. Freedom From Distractibility

Multiple R	.27
R Squared	.07
Standard Error	4.45
F	12.91
Significance of F	.0004

2. Mean CBCL Externalizing T-Score

Multiple R	.36
R Squared	.13
Standard Error	4.34
F	11.93
Significance of F	.0000

Prediction Equation:

Mean Conners = -13.59 + 4.30 (Freedom from Distractibility) + .23 (Mean CBCL Externalizing T-Score)

Table continues

Table 4 continued

Split-Half Validation (N = 84)

Variables Entered Into The Equation:

1. Freedom From Distractibility

Multiple R	.34
R Squared	.12
Standard Error	4.76
F	11.38
Significance of F	.0011

2. Mean CBCL Externalizing T-Score

Multiple R	.43
R Squared	.18
Standard Error	4.60
F	9.72
Significance of F	.0002

Prediction Equation:

Mean Conners = -18.59 + 4.80 (Freedom From Distractibility) + .30 (Mean CBCL Externalizing T-Score)

Results are similar to those above, providing preliminary validation that the FFD factor of the WISC-R and the CBCL Externalizing T-Score are helpful in prediction of stimulant response, while demographic and other variables are not.

2.a. Correlation between Parent and Teacher Conners Rating Scale is .28 ($p < .001$) ($N = 168$). Table 5 presents results of a stepwise multiple regression analysis of age, sex, neurological diagnosis, adoptive status, family structure type, socioeconomic status, Full Scale IQ, Freedom From Distractibility, Parent CBCL Internalizing T-Score, Parent CBCL Externalizing T-Score, Parent CBCL Spike, Teacher CBCL Internalizing T-Score, Teacher CBCL Externalizing T-Score, and Teacher CBCL Spike on Parent Conners Rating Scale. This examination of differences in rating source (parent vs. teacher) reveals similar results to pooled ratings. Again, the Freedom From Distractibility factor of the WISC-R is considered most significant in prediction of outcome, as measured by Parent Conners rating. The next most significant variable is Parent CBCL Externalizing score, which is consistent with pooled ratings with respect to importance of this variable. This result additionally indicates that parents are most effective at predicting parent outcome.

2.b. Table 5 also presents results of a stepwise multiple regression analysis of age, sex, neurological diagnosis, adoptive status, family structure type, socioeconomic status, Full Scale IQ, Freedom From

Table 5

Prediction of Parent Conners (N = 189)

Variables Entered Into The Equation:

1. Freedom From Distractibility

Multiple R	.23
R Squared	.05
Standard Error	5.91
F	10.96
Significance of F	.0016

2. Parent CBCL Externalizing T-Score

Multiple R	.27
R Squared	.07
Standard Error	5.86
F	7.34
Significance of F	.0009

Prediction Equation:

Parent Conners = -8.44 + 4.92 (Freedom From Distractibility) + .14 (Parent CBCL Externalizing T-Score)

Table 5 continued

Prediction of Teacher Conners (N = 173)

Variables Entered Into The Equation:

1.	Teacher CBCL Externalizing T-Score	
	Multiple R	.23
	R Squared	.05
	Standard Error	5.94
	F	9.65
	Significance of F	.002
2.	Freedom From Distractibility	
	Multiple R	.31
	R Squared	.09
	Standard Error	5.83
	F	8.90
	Significance of F	.0002
3.	Age	
	Multiple R	.34
	R Squared	.12
	Standard Error	5.78
	F	7.49
	Significance of F	.0001

Prediction Equation:

Mean Conners = -10.89 + .251 (Teacher CBCL Externalizing T-Score) + 4.41 (Freedom From Distractibility) - .34 (Age)

Distractibility, Parent CBCL Internalizing T-Score, Parent CBCL Externalizing T-Score, Parent CBCL Spike, Teacher CBCL Internalizing T-Score, Teacher CBCL Externalizing T-Score, and Teacher CBCL Spike on Teacher Conners Rating Scale.

The Teacher CBCL Externalizing T-Score was most effective in prediction of outcome (as measured by Teacher Conners rating). The Freedom From Distractibility factor of the WISC-R was again significant, but not as effective as Teacher CBCL Externalizing T-Score. In this analysis, age emerged as a third significant predictor, with older children responding best to the stimulant drug trial. It should be noted again that these relationships, although highly significant, are not large.

3. Since entering means for missing values will weaken correlation sizes, a multiple regression analysis was carried out on those cases for whom complete data was available (N = 36). Table 6 presents these results, wherein correlation sizes are significantly larger than those reported for the entire sample.

IV. DISCRIMINANT FUNCTION ANALYSES

1.a. A discriminant function analysis was performed on all cases to determine whether predictor variables (age, sex, neurological diagnosis, adoptive status, family structure type, socioeconomic status, Full Scale IQ, Freedom From Distractibility, Mean Parent and Teacher CBCL Internalizing T-Score, Mean Parent and Teacher CBCL

Table 6

Prediction of Parent and Teacher Conners for Cases with Complete Data Only (N = 36)

Variables Entered Into The Equation:

1. Freedom From Distractibility

Multiple R	.50
R Squared	.25
Standard Error	2.99
F	11.59
Significance of F	002

2. Mean CBCL Externalizing T-Score

Multiple R	.59
R Squared	.35
Standard Error	2.82
F	9.14
Significance of F	.0007

Prediction Equation:

Mean Conners = 2.87 + 3.38 (Freedom From Distractibility) +.56 (Mean CBCL Externalizing T-Score

Externalizing T-Score, and Mean Parent and Teacher CBCL Spike) could successfully discriminate between "yes" and "no" responders. For this analysis, a subject was considered a "yes" responder if either his/her parent or teacher indicated a "yes" response (as outlined above). Table 7 presents results of this analysis.

As indicated in Table 7, approximately 72% of cases could be correctly classified as "yes" or "no" responders through the utilization of Neurological Diagnosis (positively related to response), Freedom From Distractibility, Age, Mean CBCL Externalizing T-Score, and Full Scale IQ (positively related to response).

1.b. The above analysis was repeated after random split-half sampling for purposes of validation. Table 7 also presents results of this analysis. Slightly different predictor variables emerged as significant. Although Neurological Diagnosis remains most significant, Mean CBCL Spike (positively related to response), Sex (boys more likely to respond), and Socioeconomic Status (negatively related to response) were included in this discriminant function along with Freedom From Distractibility and Full Scale IQ. This provides only partial validation of the analysis presented in 1.a above.

2.a. An additional discriminant function analysis was performed to determine whether measured predictor variables (age, sex, neurological diagnosis, adoptive status, family

Table 7

Discrimination of Yes/No Responders Through Parent or Teacher Rating (N = 336)

Variables Entered Into Analysis:	Wilks	Significance
1. Neurological Diagnosis	.973	.0027
2. FFD	.957	.0007
3. Age	.944	.0002
4. Mean CBCL Spike	.937	.0002
5. Full Scale IQ	.932	.0003

Percent Correctly Classified: 72.02

Yes Responders Correct: 75.5%
No Responders Correct: 58.8%

Table continues

Table 7

Split-Half Validation (N = 163)

Variables Entered Into Analysis:

		Wilks	Significance
1.	Neurological Diagnosis	.964	.0147
2.	Mean CBCL Spike	.934	.0044
3.	Full Scale IQ	.923	.0050
4.	FFD	.910	.0048
5.	Sex	.899	.0049
6.	Socioeconomic Status	.889	.0051

Percent Correctly Classified: 80.37

Yes Responders Correct: 83.1%
No Responders Correct: 46.7%

structure type, socioeconomic status, Full Scale IQ, Freedom From Distractibility, Parent CBCL Internalizing T-Score, Parent CBCL Externalizing T-Score, Parent CBCL Spike, Teacher CBCL Internalizing T-Score, Teacher CBCL Externalizing T-Score, Teacher CBCL Spike) could successfully discriminate between "yes" and "no" responders, determined by Parent Conners Rating Scale. Table 8 presents results of this analysis.

2.b. An additional discriminant function analysis was performed to determine whether measured predictor variables (age, sex, neurological diagnosis, adoptive status, family structure type, socioeconomic status, Full Scale IQ, Freedom From Distractibility, Parent CBCL Internalizing T-Score, Parent CBCL Externalizing T-Score, Parent CBCL Spike, Teacher CBCL Internalizing T-Score, Teacher CBCL Externalizing T-Score, Teacher CBCL Spike) could successfully discriminate between "yes" and "no" responders, determined by Teacher Conners Rating Scale. Table 8 presents results of this analysis.

The analyses in Table 8 reveal that discrimination of responders through parent rating (66.97% correctly classified) was not as successful as when mean teacher and parent (72.02%) or teacher rating alone (73.21%) were utilized. In addition, unlike in the multiple regression analyses presented above, Parent CBCL Externalizing T-Score was not significant in this discriminant function. Overall,

Table 8

Discrimination of Yes/No Responders Through Parent Rating (N = 333)

Variables Entered Into Analysis:

		Wilks	Significance
1.	FFD	.984	.0202
2.	Neurological Diagnosis	.976	.0192
3.	Full Scale IQ	.969	.0168
4.	Sex	.963	.0142

Percent Correctly Classified: 66.97

Yes Responders Correct: 71.6%
No Responders Correct: 53.2%

Table continues

Table 8 continued

Discrimination of Yes/No Responders Through Teacher Rating (N = 280)

Variables Entered Into Analysis:

	Wilks	Significance
1. Neurological Diagnosis	.959	.0007
2. Teacher CBCLE Externalizing T-Score	.941	.0002
3. Age	.934	.0003
4. Adoptive Status	.928	.0004
5. Full Scale IQ	.923	.0005
6. FFD	.919	.0007

Percent Correctly Classified: 73.21

Yes Responders Correct: 77.4%
No Responders Correct: 48.9%

it appears that teacher CBCL Externalizing T-Scores are more effective than parent (or mean parent and teacher) ratings in the determination of stimulant response.

3. To explore the effect of missing values, a discriminant function analysis was carried out on those cases for whom complete data was available (N = 61). As Table 9 indicates, a) significance values are larger when only those cases with complete data are evaluated, and b) neurological diagnosis remained most sigificant, but Mean CBCL Externalizing T-Score and Family Structure Type emerged as second and third predictor variables for this selected sample.

V. ANALYSES OF "STRONG" RESPONDERS

1. Table 10 presents results of a multiple regression analysis (as in III.1.a. above) for cases with a Parent or Teacher Conners Rating Scale of 6.0 or greater. For those children who responded strongly to medication, family structure was most significant in prediction of stimulant response. Those children living with their mother alone tended to respond best to the double-blind trial. The remainder of predictor variables did not account for a significant amount of variance in the outcome measure and were therefore not included in this prediction equation.

Table 10 also presents results of a multiple regression analysis (as in III.1.a. above) for cases with a

Table 9

Discrimination of Yes/No Responders Through Parent Or Teacher Rating For Cases With Complete Data Only (N = 61)

Variables Entered Into Analysis:

	Wilks	Significance
1. Neurological Diagnosis	.763	.0001
2. Mean CBCL Externalizing T-Score	.721	.0001
3. Family Structure	.698	.0001

Percent Correctly Classified: 89.88

Yes Responders Correct: 97.4%
No Responders Correct: 86.7%

Table 10

Prediction of Parent and Teacher Conners for "Strong" Responders (Determined by Parent or Teacher Rating) (N = 108)

Variables Entered Into The Equation:

1. Family Structure

Multiple R	.27
R Squared	.07
Standard Error	3.13
F	8.47
Significance of F	.0044

Prediction Equation:

Mean Conners = 8.12 + 2.28 (Family Structure)

Table continues

Table 10 continued

Prediction of Parent and Teacher Conners for "Strong" Responders (Determined by Parent and Teacher Response) (N = 40)

Variables Entered Into The Equation:

1. Mean CBCL Externalizing T-Score

Multiple R	.44
R Squared	.19
Standard Error	2.82
F	9.03
Significance of F	.0047

Prediction Equation:

Mean Conners = -12.49 + .339(Mean CBCL Externalizing T-Score)

Parent and Teacher Conners Rating Scale of 6.0 or greater. For these children, for whom the response criteria were most stringent, the Mean CBCL Externalizing T-Score was most significant in prediction of response. This again indicates that those children rated as most active and undercontrolled by both parents and teachers tended to respond best to the drug trial. The remainder of the predictor variables were not significant and were not entered into the prediction equation.

2. Table 11 presents results of a multiple regression analysis (as in III.2.a. above) for cases with a Parent Conners Rating Scale of 6.0 or greater. Table 11 also presents results of a stepwise multiple regression analysis (as in III.2.b.) above for cases with a Teacher Conners Rating Scale of 6.0 or greater.

When evaluated separately, it is apparent that family structure is more significant in parent outcome ratings than in teacher ratings, where CBCL Externalizing T-Scores are again most significant.

VI. ANALYSIS OF CONTINUATION ON MEDICATION

Correlations of predictor variables with immediate continuation on medication after double-blind trial were carried out, as presented in Table 12. Mean CBCL Externalizing T-Score correlated most highly with the "continue" variable ($r = .4099$, $p < .001$). Mean Conners

Table 11

Prediction of Mean Parent and Teacher Conners for "Strong" Responders (Determined by Parent Response) (N = 65)

Variables Entered Into The Equation:

1. Family Structure

Multiple R	.28
R Squared	.08
Standard Error	3.28
F	5.47
Significance of F	.0226

Prediction Equation:

Mean Conners = 9.00 + 2.56 (Family Structure)

Table continues

Table 11 continued

Prediction of Mean Parent and Teacher Conners for "Strong" Responders (Determined by Teacher Response) (N = 83)

Variables Entered Into The Equation:

1. Teacher CBCL Externalizing T-Score

Multiple R	.33
R Squared	.10
Standard Error	3.19
F	9.56
Significance of F	.0027

Prediction Equation:

Mean Conners = -9.88 + .27 (Teacher CBCL Externalizing T-Score

Table 12

Correlation of "Continue" With All Variables

	r	N
Demographic Variables		
Sex	.0712	336
Age	-.1033	336
Neurological Diagnosis	-.0106	290
Adoptive Status	-.0225	306
Family Structure Type	.0327	312
Socioeconomic Status	.0040	249
IQ Variables		
FSIQ	-.0880	155
VIQ	-.1171	154
PIQ	-.1008	154
FFD	-.0617	125
CBCL Variables		
Parent CBCL Externalizing	.2722**	168
Parent CBCL Internalizing	.1403	168
Parent CBCL Spike	.2177**	168
Teacher CBCL Externalizing	.3240**	123
Teacher CBCL Internalizing	-.0418	123
Teacher CBCL Spike	.0852	123
Mean CBCL Externalizing	.4099**	117
Mean CBCL Internalizing	.1003	117
Mean CBCL Spike	.2255*	117
Conners Rating Scale		
Parent "Yes/No" Rating	.3402**	333
Teacher "Yes/No" Rating	.3183**	280
Parent Numerical Rating	.2999**	189
Teacher Numerical Rating	.3183**	173
Mean Numerical Rating	.3937**	168

* $p < .01$
** $p < .001$

rating and "continue" correlated at r = .3937, p < .001. Although significant, these correlations are modest in size - particularly with regard to expected values. No demographic or IQ variables were significant with respect to their correlation with continuation on medication.

VII. INTERACTIONS

1. A graphic representation of CBCL-Externalizing T-Score by gender effects is presented in Figure 1. This figure indicates no interaction effect, with an almost parallel relationship between males and females on the CBCL-E measure. A significant main effect for CBCL-E (F = 7.916, p = .005), a non-significant main effect for sex (F = 1.324, p = .252), and a non-significant interaction of CBCL-E by sex (F = .000, p = .993) resulted. When the interaction is entered into a multiple regression analysis for prediction of stimulant response, results are unchanged from those presented above.

2. A graphic representation of age by gender effects is presented in Figure 2. This figure indicates no effect for age (F = .095, p = .758), no effect for sex (F = .811, p = .369), and no interaction effect (F = .397, p = .530).

3. A representation of socioeconomic status by family structure type is presented in Figure 3. Again, interaction effects are not significant (F = .268, p = .605). Socioeconomic status is also not significant (F = .204, p =

FIGURE 1.
Diagnosis and Gender Effects

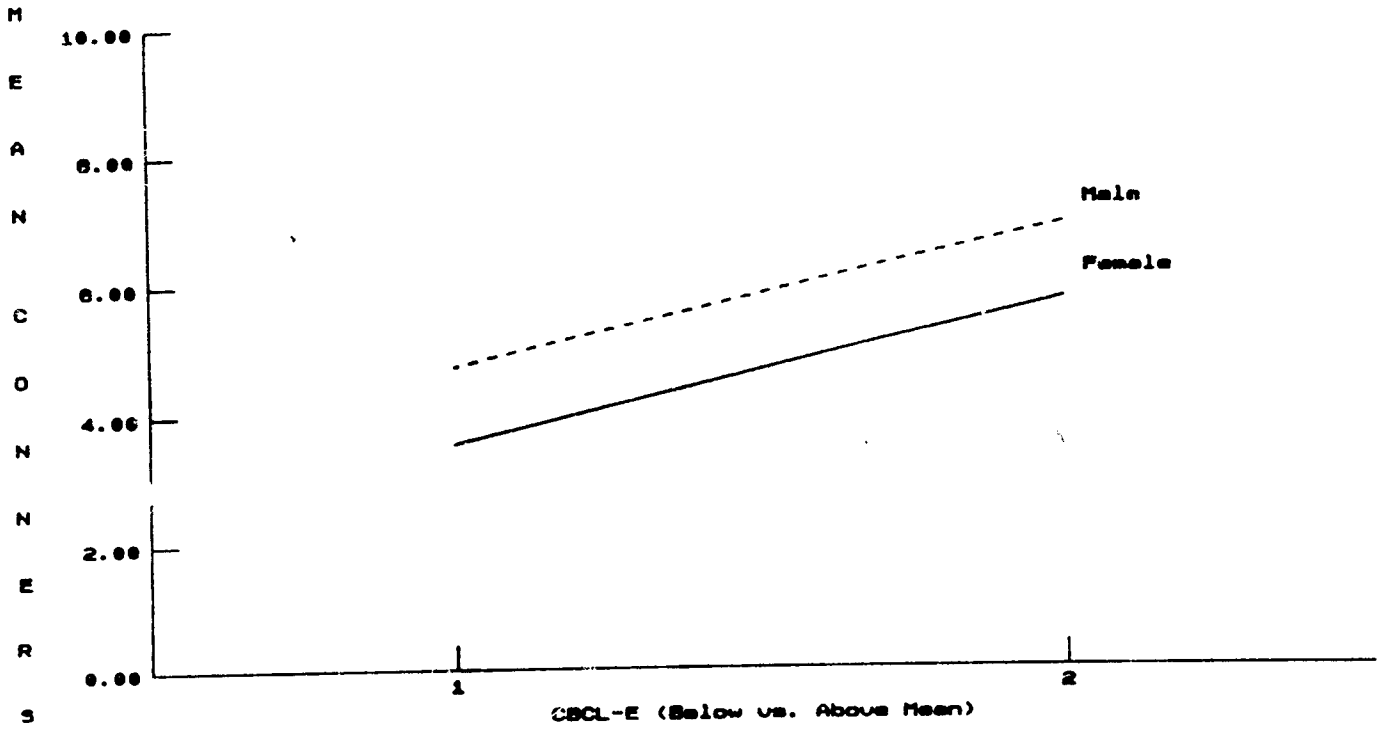


FIGURE 2.
Age and Gender Effects

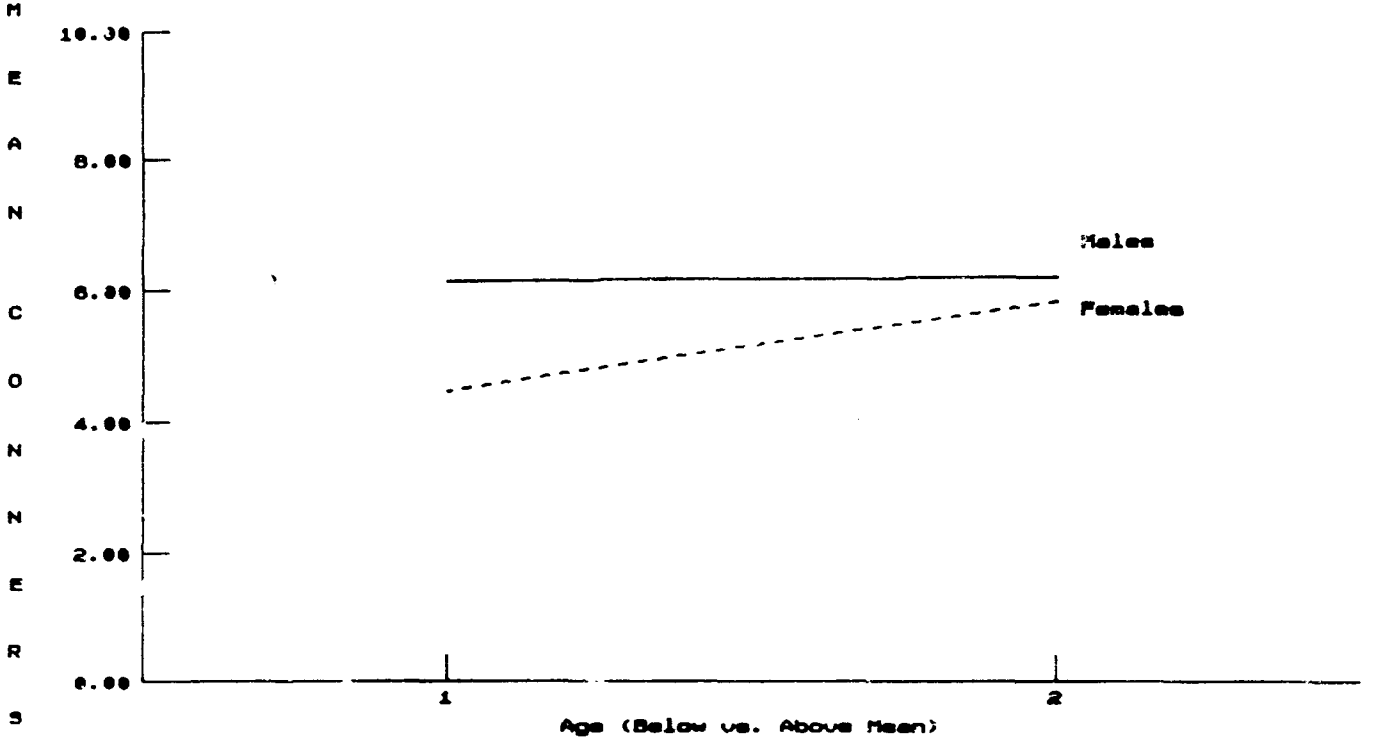
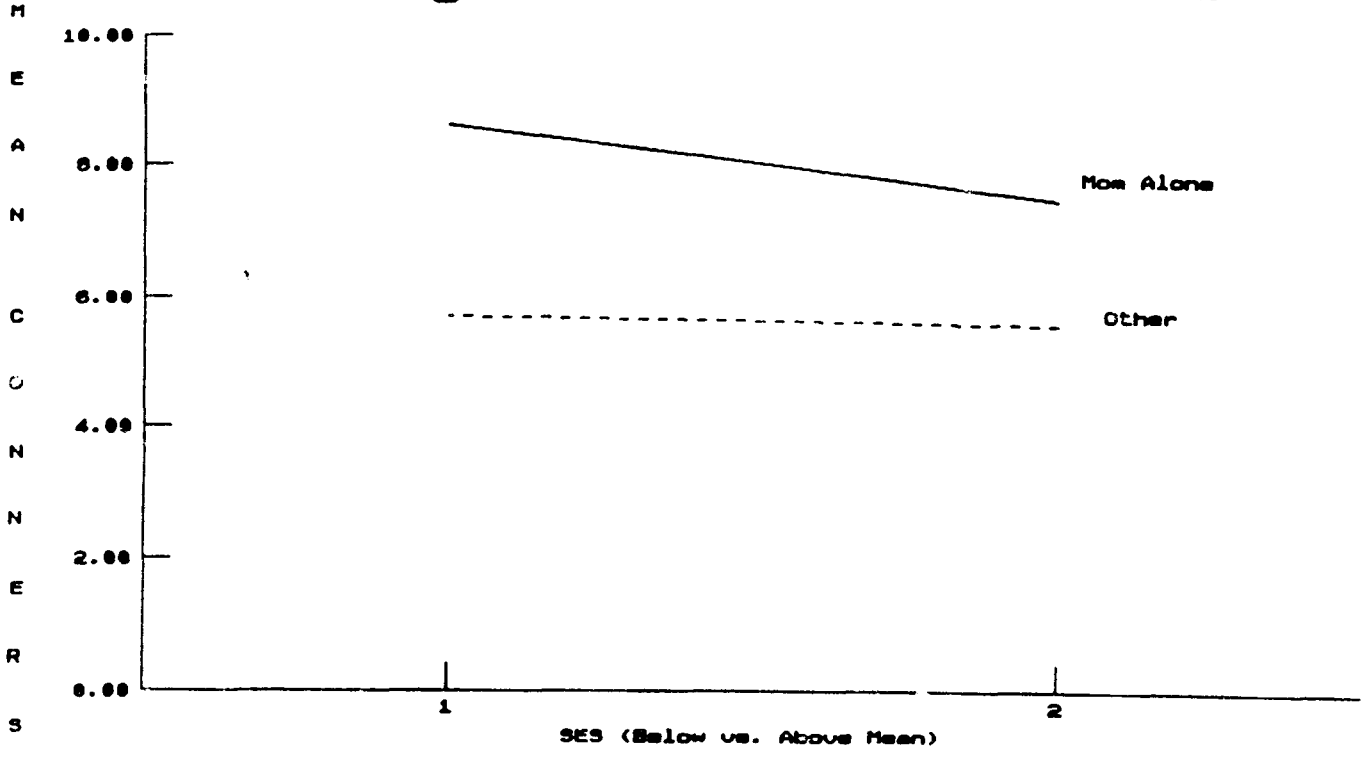


FIGURE 3.
Family Structure and SES Effects



.652). Family structure type is significant (F = 6.770, p = .010), with children living with their mothers alone more likely to respond to medication than those living in other family structure types.

VIII. FOLLOW-UP DATA ANALYSES

1. Table 13 presents data collected through telephone follow-up. Two variables were employed for evaluation of outcome at this interview: 1) continuation on medication (yes/no), and 2) for those children still taking stimulants, caretakers were asked to rate change in attentional and non-compliant behavior (much worse, worse, same, better, or much better). These variables were ultimately combined into one dichotomous variable due to lack of variance (all children who were still taking medication were rated by their caretaker as "much better" since being placed on stimulants). Information regarding side effects was also noted. Two children were reported to have significant side effects from the medication. One child (continued on medication) reportedly had insomnia; another child became irritable with methylphenidate and, although he responded well, was taken off the medication approximately two months after the double-blind trial. Two other caretakers reported side effects (irritability and depression, respectively), but their children had remained on medication.

Table 13

Follow-Up Data

#	Initial Age	Initial Parent Rating	Initial Teacher Rating	Age at Follow-Up	Status at Follow-Up
1	7.86	Yes	Yes	10.67	Continued
2	11.72	Yes	Yes	15.26	Not Continued
3	9.96	Yes	Yes	11.73	Continued
4	10.97	Yes	Yes	12.62	Continued
5	8.37	Yes	Yes	11.02	Continued
6	6.30	Yes	Yes	9.84	Continued
7	8.88	Yes	Yes	10.70	Continued
8	9.92	Yes	No	11.51	Not Continued
9	7.11	Yes	Yes	8.20	Continued
10	7.56	Yes	Yes	9.20	Continued
11	9.41	Yes	Yes	10.45	Continued
12	7.54	Yes	Yes	10.62	Continued
13	11.75	No	Yes	13.49	Continued
14	7.56	Yes	Yes	9.09	Continued
15	8.06	Yes	No	9.18	Continued
16	13.07	Yes	No	16.61	Not Continued
17	15.02	No	No	18.54	Not Continued
18	11.88	Yes	Yes	15.95	Continued
19	4.87	Yes	Yes	8.38	Continued
20	9.48	Yes	Yes	11.02	Not Continued
21	11.16	Yes	Yes	12.68	Not Continued
22	7.96	Yes	Yes	10.87	Continued
23	7.61	Yes	Yes	10.38	Continued
24	8.25	Yes	Yes	10.95	Continued
25	6.55	Yes	Yes	10.57	Not Continued
26	7.87	No	Yes	10.50	Not Continued
27	11.10	Yes	Missing	12.82	Continued
28	6.71	No	No	10.25	Continued
29	7.18	Yes	Yes	8.29	Not Continued
30	8.74	Yes	Yes	9.78	Continued
31	9.06	Yes	Yes	11.68	Continued
32	9.08	No	Missing	15.85	Not Continued
33	5.26	No	Yes	8.34	Not Continued

SUMMARY TABLE:

Initial Age: Mean = 9.21 S.D. = 2.59
Age at Follow-Up: Mean = 11.73 S.D. = 2.97
% Positive Initial Parent Response: 81.8
% Positive Initial Teacher Response: 78.8
% Continued at Follow-Up: 63.6

Table continues

Table 13 continued

Follow-Up Data

Note: One child was not taking medication at the time of the interview due to a decision by her caretaker and physician that a temporary "break" was needed in order to evaluate difficulty sleeping. Her caretaker stated that, when on the medication, she was a strong responder and her attention was "much better". This child was included in the "continued/much better" group, even though she was not taking medication at the time.

A *t*-test was used to determine whether those children who had most recently completed the double-blind trial would be most likely to have continued on medication. This test was not significant ($t = 1.08$, $p = .287$).

To further explore age effects, a chi-square analysis is presented in Table 14. This table indicates that children in adolescence are not significantly different than children under the age of 12 with respect to continuation on medication at follow-up.

A discriminant function analysis was carried out for the following groups: a) subjects who responded to the double-blind trial as rated by either parent or teacher and who continued on medication at follow-up (N = 20) and b) subjects who did not respond to the double-blind trial as rated by either parent or teacher and who did not continue on medication at follow-up (N = 2). Results are presented in Table 15.

Results of this analysis are similar to those presented above, with neurological diagnosis, Freedom From Distractibility, and age emerging as significant predictor variables. It is apparent that prediction is more powerful when both immediate and longer-term outcome measures are utilized, with 100% of cases being correctly classified in this small sample. Further research in other samples will be necessary to validate this result.

Table 14

Chi-Square: Age by Continuation on Medication at Follow-Up (N = 33)

	Continued	Not Continued	TOTAL
Less than 12 years	16	7	23
Greater than 12 years	5	5	10
TOTAL	21	12	33

Pearson correlation = .28

Table 15

Discrimination of Yes/No Responders Through Parent or Teacher Rating and Follow-Up Interview (N = 22)

Variables Entered Into Analysis:

	Wilks	Significance
1. Neurological Diagnosis	.524	.0004
2. FFD	.275	.0000
3. Age	.226	.0000
4. Sex	.184	.0000
5. Adoptive Status	.172	.0000

Percent Correctly Classified: 100.0

Yes Responders Correct (N = 20): 100.0%
No Responders Correct (N = 2): 100.0%

2. A chi-square analysis was carried out to test the hypothesis that children who responded strongly (parent or teacher Conners' rating of greater than or equal to 6.0) to the medication trial would be most likely to continue on medication at longer-term telephone follow-up. Table 16 presents results of this analysis.

A significant relationship does not exist between these two variables in the direction hypothesized; children who responded most strongly to medication were not necessarily those who continued on medication on follow-up. Factors other than results of the double-blind medication trial are apparently operative in the decision both to initially medicate the child and to continue with the medication.

Table 16

Chi-Square: Strong Response by Continuation on Medication at Follow-Up (N = 28)*

	Continued	Not Continued	TOTAL
Strong	6	3	9
Less than Strong	6	13	19
TOTAL	12	16	28

Chi-Square = .08

*Five cases are missing from this analysis due to missing objective Conners ratings.

PART E

DISCUSSION

I. SUMMARY OF HYPOTHESES

1. Primary Hypotheses: Neurological status, WISC-R Freedom From Distractibility, age, and sex will be significantly related (in that order) to the primary criterion variable (mean Conners rating), while family constellation type, SES, and CBCL measures will not account for a sigificant amount of variance in the outcome measure.

a) A step-wise multiple regression analysis revealed that the Freedom From Discractibility factor of the WISC-R and the Mean CBCL Externalizing T-Score were most significant for prediction of Mean Conners rating (medication response). Other predictor variables did not account for a significant amount of variance in Mean Conners rating.

These results are consistent with the findings of Barkley (1976), McBride (1988) and Taylor, et al. (1987), indicating that initial measures of attention are most effective in determining medication outcome. In this sample, those children demonstrating difficulty sustaining attention to tasks (as measured by the Freedom From Distractibiity factor of the WISC-R) and those rated by parents and teachers as demonstrating "aggressive, antisocial, and undercontrolled" behaviors (as measured by the CBCL Externalizing factor) tended to respond most favorably to the stimulant drug trial.

As noted above, these relationships are significant ($p < .001$), but actual correlation sizes are relatively small. Prediction equations should therefore be recognized as guidelines, rather than absolute indicators of outcome in individual clinical cases. In addition, these relationships must be validated in other samples (preferrably in samples with only limited missing data) before conclusions can be drawn regarding predictive utility.

b) When all cases are included for discriminant function analysis, less sensitive prediction is possible. Discriminant function analysis revealed that Neurological Diagnosis, Freedom From Distractibility, Age, Mean CBCL Spike, and Full Scale IQ were significant for discrimination of "yes" and "no" responders. Discrimination was successful for 72.02% of cases.

When the criterion variable was coded dichotomously, dichotomous predictor variables (Neurological Diagnosis, Freedom From Distractibility, Mean CBCL Spike) became more successful for prediction. In this sample, the presence of a neurological diagnosis was significant for prediction of good drug trial response; those children who had a neurological diagnosis tended to respond better to medication. This supports the hypothesis that stimulant medication somehow "normalizes" a malfunctioning nervous system, as noted above. Freedom From Distractibility (FFD) continued to be successful for prediction; a poor score on

this measure was predictive of poor medication response. In this analysis, age was also entered into the discriminant function; older children tended to respond best to medication. The presence of a T-score greater than 70 on any scale of the CBCL (Mean CBCL Spike) also was significant; children with the presence of a CBCL Spike tended to respond best to medication.

Considered as a whole, results of this analysis again indicate that the more severe the neurological/attentional difficulty, the better the child tends to respond to medication. The size of these correlations, although statistically significant, are again nominal in size.

2. Secondary Analyses:

a) Source Analyses: It was hypothesized that results would remain stable, regardless of rater source (parent vs. teacher).

These analyses indicated that overall, CBCL Externalizing and FFD scores were most significant for the prediction of outcome, whether rated by parents or teachers. These results indicate that, at least with regard to medication response, the source of information (parent vs. teacher) is not a relevant variable. When predicting outcome as rated by parents, parent predictor variables were more correlated than teacher variables and vice versa. This result was to be expected, given the situational specificity

of some hyperactive behaviors (Johnson & Prinz, 1976; Landman & McCrindle, 1986; Langhorne, Loney, Paternite, & Bechtoldt, 1976).

One exception emerged in the discriminant function analysis for prediction of strong "yes/no" response as determined by parent or teacher and parent rating alone. For these analysis, family structure type emerged as the most significant prediction variable; those children who lived with their mother alone (as opposed to other family situations) were most likely to respond to medication, with this variable outweighing all others in this particular analysis.

b) Strong Responders: It was hypothesized that significant predictor variables would remain stable, but that these variables would account for more variance in mean Conners rating of the "strong" responders.

It was important to evaluate "strong" responders separately, since even an equivocal response was rated a "yes" response in the initial analyses. For those children who responded strongly to the drug trial, family structure type emerged as an important predictor variable for parental ratings. For this sample, children living with their mother alone tended to demonstrate the strongest response to medication, as rated by their mothers. When teacher ratings are entered into these analyses, the CBCL Externalizing T-Score lessens the effect of family structure and again

accounts for most variance.

Two hypotheses are generated by this result: a) mothers raising their ADHD children alone are more likely to perceive changes in their child's behavior due to stimulant drugs, and/or b) children raised by their mothers alone are more likely to respond strongly to stimulant drugs. With regard to the latter hypothesis, it is possible that the single parent family structure type lends itself to more consistency with drug administration and/or parenting techniques, which could have a beneficial effect on ADHD children. More research will be needed to evaluate these relationships in full.

When both parent and teacher rate the child as a "strong" responder, CBCL Externalizing T-Score becomes a significant and more meaningful variable than when predicting "yes/no" responders, accounting for 19% of variance in Mean Conners rating. This result partially supports hypothesis 2.b: prediction of strong responders is more powerful than prediction of those who respond more equivocally. However, actual predictor variables did change, with freedom from distractibility no longer accounting for a significant amount of variance.

c) Continue Variable: It was hypothesized that the correlation between the outcome of the double-blind trial and the "continue" variable (whether or not the child was placed on medication) would be very high and significant

at p<.001.

An unexpected result emerged in this analysis. Although Mean Conners rating did correlate significantly with placement on medication after the drug trial ($r = .3937$, $p < .001$), this correlation was not of the magnitude expected. In fact, the Mean CBCL Externalizing T-Score (collected before the drug trial) actually correlated higher with continuation on medication ($r = .4099$, $p < .001$).

Since the primary purpose of collecting Conners ratings is to determine the success of the double-blind trial (hence, to proceed/not proceed with medication), one would expect this correlation to be exceedingly high (near perfect). Instead, only approximately 15% of variance in the continue measure is accounted for by Conners ratings. It is apparent that other, more subjective factors are entering into the medication decision to a highly significant degree (e.g., parental attitudes toward medication, clinician's impressions regarding compliance, child's opinion regarding stimulant treatment, presence of side effects). It will be important to evaluate the relative weight of these factors.

d) Interaction effects: It was hypothesized that boys without the presence of aggressive/non-compliant symptoms would respond best to stimulant medications. Age and gender interactions, as well as family constellation type and socioeconomic status interactions, were also hypothesized.

Interactions of externalizing symptomatology by gender, age by gender, and family structure type by socioeconomic status were not significant in this sample.

3. Follow-Up Data Analyses:

a) It was hypothesized that significant predictor variables would not change, but that prediction would be more powerful when follow-up data was included as part of the outcome measure.

A discriminant function analysis for subjects for whom follow-up data were available revealed that prediction was much more powerful when both the short-term (Conners rating) and longer-term (telephone interview) variables were used, with 100% of cases correctly predicted. Neurological diagnosis, Freedom From Distractibility, and Age were again the most significant predictor variables for this discriminant function.

Response bias must be considered in this sample, since it is possible that parents who had a positive experience with stimulant medication would be more likely to respond for a follow-up interview.

b) It was also hypothesized that those subjects who were classified as "strong" responders on initial drug trial would be more likely to remain on medication at follow-up.

Chi-square analysis did not support the hypothesis that children who were "strong" responders were more likely to remain on medication at follow-up. This analysis lends support to the finding that factors other than the results of the medication trial (as determined through parent and teacher Conners ratings) are playing a significant role in whether a child is continued on medication.

c) It was nypothesized that children who experienced side effects would be less likely to continue on medication at follow-up.

The presence/absence of side effects also was indicative of those who remained on medication. Although four children reportedly experienced significant side effects to methylphenidate, three of those children continued to take medication on follow-up.

II. LIMITATIONS

The limitations of this study are as follows:

1) Retrospective Design: Although retrospective research is often utilized and serves to generate important experimental hypotheses, a prospective design is almost always preferable when attempting to make confident conclusions.

For example, evaluation of certain specifications was not possible due to the retrospective nature of this study. In order for a child to undergo a double-blind stimulant medication trial, the child is required to meet DSM criteria for ADHD. Due to the variety of clinicians treating these children, however, it was not possible to monitor the degree to which these criteria were met.

2) Data Limitations: Conclusions are also tempered by the following data limitations:

a) Data were collected from a variety of sources, each with their own reporting style. This led, for example, to the issue of differing outcome measures (continuous vs. dichotomous).

b) Data were often unavailable. Although it was assumed for purposes of this research that cases with missing data did not differ from those without (with the exception of FSIQ), this assumption could only be tested in a limited manner by comparing analyses of complete cases with those containing missing values. The issue of missing data is an important one in the present research, due to the number of cases with at least one missing value. Although data were assumed not to be systematically missing, there is no statistical analysis available to test this assumption.

c) Response bias in follow-up data. It is possible that several response biases exist in follow-up data: parents who had a good experience with the stimulant

drug trial, parents who had more available time, parents with higher socioeconomic status, or parents who are more involved in their children's medical status may have been more likely to respond to the request for follow-up telephone interview. These biases may have differentially affected outcome and, in future studies, a shorter follow-up period with more intensive recruitment should be utilized.

3) Predictor Variables: Due to the retrospective nature of this study, predictor variables were not optimally defined. Neurological diagnosis, for example, would have been more meaningful if collected from a complete neurological examination of each child.

4) Outcome Measure: Although the parent and teacher Conners rating scales have been consistently utilized to determine outcome in previous research, they do not cover a broad range of behaviors. Collection of a direct measure of attentional ability or a more comprehensive rating scale would be valuable in this regard.

III. SUGGESTIONS FOR FURTHER RESEARCH

Several interesting avenues for further research emerged from these data.

1) The relationship between family structure and stimulant response deserves further exploration. From this study, it appears that those children who live with their

mothers as the sole parental figure respond (or are perceived to respond) stronger to stimulants (as rated by their mothers). It could be hypothesized, for example, that mothers raising their ADHD children alone are more sensitive to changes in their child's behavior, or that these children are more likely to show medication effects in their mother's presence.

2) Evaluation of the same variables in a new sample will also be needed to validate these results.

3) An important question, beyond the scope of this study and not addressed in the previous literature, is that of compliance. Since caretakers only variably comply with clinicians' directions, this could have a significant effect on eventual outcome. Although difficult to quantify, it will be important in future research to assess caretaker compliance with regard to stimulant responsivity.

4) Since the Externalizing factor of the CBCL was an integral predictor variable in this sample, an evaluation of the subscales constituting this factor (delinquent, hyperactive, aggressive) would be valuable in future research investigations. For the present research, this was not evaluated due to the low number of data points on each of these subscales; the Externalizing factor was felt to be more reliable. It would be interesting in future studies to explore these subscales individually; it is possible, for example, that the hyperactive subscale would best predict

medication response.

5) An additional area needing further research is the motivation of parent, teacher, and clinician for placing a child on medication. Contrary to expectation, the results of this research indicate that the outcome of the double-blind trial is not an overwhelming factor in this decision process. It would be useful (particularly in the clinical realm) to determine what other influences are functioning in this decision.

6) In the follow-up portion of this study, information with regard to concurrent alternate treatment(s) (e.g., behavior therapy, parent training) was not collected. This information would be important to address in any further research, since it is likely that the presence of these treatments would differentially affect outcome.

7) Since ADHD children's symptomatology and responses to stimulant medication are so varied interindividually, the utilization of single subject design would be particularly valuable for future research in this area.

IV. CONCLUSIONS

Overall, the results of this study indicate that children demonstrating the highest levels of hyperactive and inattentive behavior on presentation to the clinic setting are most likely to respond positively to a double-blind

stimulant medication trial, as rated by both parents and teachers. Results of this study contribute to the existing literature, supporting Barkley's (1976) assertion that those children highest in activity level and inattention will tend to respond most favorably to stimulant drugs, while demographic, familial, and neurological variables are not as highly significant in prediction of responses.

It is possible that the most hyperactive children were merely perceived to benefit the most. Less active children may have benefited the same amount objectively, but this benefit was not rated as dramatically by parents and/or teachers. Future research is called for to address this question, wherein pre-and post- measures of attention are collected in order to obtain an objective measure of attentional change.

Although results are consistent and highly significant, the strength of the relationships are only of limited meaning clinically. These variables can only partially explain stimulant responsivity, and although tendencies are slowly being determined, it appears unlikely that prediction of response in individual cases will be possible without an actual drug trial.

PART F

APPENDICES

Children's
Hospital & Medical Center

October ___, 1991

Dear Parent or Guardian:

Your child was evaluated at our hospital for possible Atttention Deficit Hyperactivity Disorder (ADHD). I hope this was a useful service to your family.

As you know, Children's Hospital and Medical Center is a teaching and research institution as well as a provider of patient care. As such, patients who are treated at Children's are sometimes invited to participate in confidential, entirely voluntary research studies. These research projects help further our understanding of various childhood disorders in the hope of providing better medical care.

Jennifer Thomson, M.S., a Ph.D. student at the University of Victoria, is currently studying patients who have undergone a double-blind stimulant medication trial for the treatment of ADHD at Children's. Ms. Thomson is attempting to determine which factors, if any, can predict a good response to medication (e.g., sex, age, neurological status, etc.). Since, according to our records, your child underwent such a trial, I would like to invite you to participate in this study.

Participation in the study involves a "one-time only," brief (approx. 5 minutes) telephone conversation with Ms. Thomson regarding how your child is doing now. All information will be kept confidential and will not be entered into your child's medical file.

If you are interested in learning more about this study, please return the enclosed postcard addressed to Ms. Thomson. Return of this postcard does not automatically enroll your child in the study; it just states that you agree to be contacted. When contacted, you will be told more information about the study and will have the opportunity to ask questions. If you have questions before returning the postcard, please feel free to contact Jennifer Thomson at 368-4949.

4800 Sand Point Way N.E. PO Box C5371 Seattle Washington 98105 206 526-2000

I hope that you and your family are doing well.

Sincerely,

Christopher K. Varley, M.D.
Head, Pediatric Psychopharmacology Service
Department of Child Psychiatry, CHMC

APPENDIX B

PARENT/GUARDIAN FOLLOW-UP QUESTIONNAIRE
Stimulant Response Study

Patient Name: _____ ID#: _____

Guardian Name: _____ Phone: _____

Relationship to Pt: _____

Continued on Meds? _____ Yes _____ No _____ Other

Comments _____

_____

_____

_____

_____

_____

IF STILL ON MEDS:

Improvement Rating:
1=Much Worse
2=Worse
3=Same
4=Better
5=Much Better

Home Behavior
- aggressive/non-compliant _____
- inattentive _____

Overall Functional Rating _____
now, compared to status
before initiation of
medication

Comments _____

_____

_____

PART G

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