A Review of Research with Benzedrine, Dexedrine, and Ritalin on the Hyperkinetic Behavior Syndrome

William J. Hampstead

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A REVIEW OF RESEARCH
WITH BENZEDRINE, DEXEDRINE, AND RITALIN
ON THE HYPERKINETIC BEHAVIOR SYNDROME

by

William J. Hampstead

A Thesis
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INTRODUCTION

Chemotherapy is a term applied to the use of a medicinal drug with the intent of alleviating a diagnosed acute illness or chronic disease. As applied to a form of therapeutic intervention directed toward children exhibiting the symptomatology of the hyperkinetic behavior syndrome, chemotherapy appears to have been a relatively hit or miss affair. Consequently, the concept of a medicinal drug in relation to these children has been severely criticized by various segments of society who have a personal interest in the subject, such as teachers, parents, and physicians. The lack of concrete knowledge of the implications involved in the use of psychotropic agents has shrouded the use of central nervous system stimulants in an air of mystery, hope, and fear. This fact has caused heated and generally unproductive arguments among professionals within the service fields as well as among lay persons.

The intent of this paper is twofold. One aspect to be demonstrated is the evolution of research in this area. Evolution of research methodology includes a slow refinement of diagnosis and specification of symptoms with a consequent improvement in research designs. The other aspect to be considered is the logical approach to the use of stimulants with hyperkinetic children, based on research, and to point out some research issues which must be investigated to use these drugs even more effectively in the future. The review will deal specifically with three stimulants: Benzedrine,
Dexedrine, and Ritalin, a description of which will follow. The time span to be covered will be approximately twenty-three years, 1950 - 1973, with the Bradley studies (1937, 1940) included as the only exceptions. These two studies are included because they are the first ones of their kind in which a central nervous system stimulant is used with a population of children generally fitting the diagnosis of hyperkinesis.
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DESCRIPTION OF THE HYPERKINETIC BEHAVIOR SYNDROME

The terms hyperkinetic, hyperactive, hyperkinetic impulse disorder, minimal brain dysfunction (MBD), and cerebral dysfunction have been utilized by parents, teachers, physicians, and other professionals in the helping services to describe behaviors which are emitted in excess of socially acceptable levels and which appear to be inappropriate for the given situation. The diagnosis of hyperkinetic reaction of childhood (adolescence) has been used as if it were a tangible, empirically proven category that provides a scientific explanation of its etiology and firm recommendations for its treatment. At this time the diagnostic category used as reference cannot supply reliable evidence as to the cause nor the most beneficial form of treatment. At best it can supply only a global description of the observable behaviors which have come to be considered as representative of this syndrome.

The Diagnostic and Statistical Manual of Mental Disorders (D.S.M. - II) (1968) describes the hyperkinetic reaction of childhood as a category which is characterized by overactivity, restlessness, distractability, and short attention span occurring primarily in younger, pre-puberty children. The determination of whether these behaviors are the result of pre- or post-natal organic brain damage or environmental factors, such as a family life in which interpersonal relationships have been disrupted by frequent moves from one locality to another, or in which one or both of the parents are themselves emotionally unstable, is left up to the person making
the diagnosis. Consequently, depending on who evaluates the child's behavior, he may be wrongly labeled as organic rather than psychogenic and, unfortunately, this label often determines the course of the child's remaining life. Treatment is dependent upon diagnosis. An inadequate parent and especially an inadequate teacher is more likely to resort to labeling a child as hyperkinetic simply due to his own inability to cope with the child's behavior and his own emotions. A conclusion which must logically follow is that evaluation of causative factors must be done on an individual basis for each child by a professional, usually a psychologist, pediatrician, and/or a psychiatrist, skilled in the utilization of the tools capable of making this diagnosis.

Description of the hyperkinetic behavior syndrome has been advanced by a number of researchers within their respective studies (e.g., Laufer, 1957; Eisenberg, 1966; Stewart, 1970; Wikler, 1970; Bell, 1972; Werry, 1972; Groover, 1972; Reece, 1973). However, due to the undetermined etiology of this syndrome, diagnosis has basically depended upon the subjective observation of the child exhibiting behaviors which were symptomatic and chronic in occurrence. Currently, emphasis is also being placed on more objective psychological and neurological evaluations in addition to the observed behaviors (Connors, 1963, 1970, 1973).

Burks (1960) lists seven symptoms which may be used as a basis for describing the behavior of a child who appears to fit into this diagnostic category of hyperkinesis. The symptoms are: "...short attention span, restlessness and overactivity (motor-
driveness), poor judgment and impulsive action, low frustration
tolerance and irritability, poor perceptual and conceptual abilities
(reflected in serious academic deficiencies), defective memory, poor
muscular coordination (p. 18)."

Little modification of the basic description of the syndrome
has occurred outside of further delineation of the specific
behaviors involved and their social consequences. Groover (1972)
describes the hyperkinetic child as:

"...a youngster, usually male, who is overly active for his
age and whose actions are often impulsive, random, purpose­
less, and at times perseverative. His attention span is
strikingly short; he appears to flit from one task to an­
other, completing few. He is easily distracted, seemingly
responding to each and every stimulus in his environment.
His emotional swings are great, so that he is overly
affectionate one moment and biting and kicking the next.
He appears to test continually the limits of his environs
and seems oblivious to punishment (pp. 37, 41)."

He goes on to indicate the general consequences of such behavior in
terms of parental, educational, and peer relations to the hyper­
kineic child's excessive and irritable behavior. There is a
general frustration experienced by all who come into contact with
the child when their efforts to educate, discipline, or interact
fail. After consistent repetitions of the same consequences, the
normal reaction is to isolate the child by excluding him from the
group, i.e., peer or educational, and to respond in a punishing
manner. The punishing manner may include anything from attempts at
physical discipline such as spankings, to simply discounting his
presence as much as possible. The ultimate result of this course of
action is to insure that the child experiences a developmental lag
in academic and interpersonal skill situations which may account for the immature behavior patterns overtly observable.

Bell (1972) elaborated on the general conceptualization of the syndrome when he developed a rating scale for pre-school and kindergarten children. The rating scale focuses on the specific behaviors that may distinguish the hyperkinetic child from other children. Here also, the child must consistently demonstrate the behaviors used as a basis for assessment. The general symptoms are elaborated within these behaviors and therapeutic improvement would be a significant lessening of these symptomatic behaviors. The overt behaviors used to identify the hyperkinetic child are:

Frenetic Play (Frantic)
The hyperkinetic child, "much more than other children overtly demonstrates impulsive, rapid, ineffective, and incomplete play."

Induction to Intervention
The hyperkinetic child, "plays in such a way as to make it likely that a teacher in the area would feel compelled to intervene either to prevent injury to the child or others, or to prevent damage to physical objects."

Inability to Delay
The hyperkinetic child, "when waiting for food, toy or any other object which is of interest, or when waiting to take part in an activity, seems unusually unable to wait for gratification."

Emotional Aggression
The hyperkinetic child, "frequently throws toys, tears things down, breaks toys, pushes objects over, attacks, pushes, or hits, takes things from others even though not needed to achieve an objective or even though he may or may not be upset."

Nomadic Play
The hyperkinetic child, "shifts attention rapidly from one setting or toy to another, typically trying out an item for only an instant and then moving on, showing no sustained play or engagement of interest unless assisted."

Spilling, Throwing
The hyperkinetic child, "spills water, containers, salt and other
substances, and/or throws food or other objects much more often than others (playful throwing of a ball should not be considered under this heading) (pp. 26-27)."

While the basic description of the hyperkinetic behavior syndrome has been used for a number of years, the concern over specification of functionally descriptive behaviors, within the syndrome, is a more recent occurrence, c. 1963. The trend toward exactness and practical utility of a descriptive diagnostic category is the product of continual research conducted on many levels of therapeutic intervention, e.g., chemotherapy, behavior modification, and various modes of group therapy.

The area that possibly holds the most potential for illuminating not only the type of treatment most beneficial for the individual child, but also of providing some insight into the etiology of the syndrome and the differentiation of overlapping diagnostic categories is chemotherapy. Of particular importance in this respect are the data being gathered and analyzed from research done with amphetamine-based central nervous system stimulants, such as Dexedrine and from the distantly related stimulant, Ritalin. This is not to imply that the research being done with tranquilizing agents, such as chlorpromazine and thioridazine, is without merit; rather that the work done with stimulants appears to be headed in the direction of identifying both behavioral and neurophysiological groupings of children who may respond more readily to a particular approach. The general consensus gleaned from the research literature implies that there is no single treatment modality which may be universally applied to all hyperkinetic children. For some children,
stimulants facilitate an improvement on academic and behavioral levels; for others, tranquilizers accomplish the same goals. Other hyperkinetic children may not be benefited by either type of chemical agent; yet group therapy dealing with the expression of emotions may be most beneficial for them. The point of major importance is the fact that despite the many prejudices leveled against it, chemo-therapy has pointed out new directions for treatment other than drugs when such an approach is most appropriate for the individual child. It has accomplished this through constant evaluation of research methodology and through the necessity for concreteness in describing drug effects and in establishing empirically the reasons for success or failure with any individual child.
Amphetamines are sympathomimetic amines with central nervous system stimulant activity. These agents reproduce the effects of impulses conveyed by the various fibers of the sympathetic nervous system. Thompson (1967) describes the function of this segment of the nervous system as being responsible for the mobilization of bodily resources for emergencies, e.g., increased rate of heart beat, inhibition of non-essential bodily functions, such as the digestive action of the stomach, and increased sensitivity to incoming stimuli. Consequently, while all amphetamines have this same basic method of action, the details and intensity of their effect vary widely due to the chemical composition of the amphetamine-derived compound used and the specific neural pathways which it activates.

Smith, Kline & French (1966) describe Dexedrine as the dextro-isomer of the dl-amphetamine sulfate (Benzedrine). It has a marked selective action, due to the particular nerve fibers which it activates in the child's nervous system, which moderates problem behavior, such as impulsivity, aggressivity, and mood swings. Dexedrine has been demonstrated to have a beneficial effect on the attention span and, when used as indicated, has not shown any ill-effects over long term therapy; however, Safer (1973) has found exception to this and his data are discussed in the section on side effects later in this paper. Dexedrine is a psychomotor stimulant which produces the desired central nervous
system stimulation at lower doses than the mixture of levo- and
dextroamphetamine (Benzedrine). The levo-isomer of the mixture has
been considered to be a neutral contaminant which neither increases
nor decreases the effectiveness of the dextro-isomer. However, when
administered in the combined form, i.e., Benzedrine, higher dosage
levels must be utilized before the dextro-isomer can moderate the
behavior to the same extent as when it is administered in its purifi-
ed form. Dexedrine is approximately twenty times as potent as
Ritalin. While Dexedrine produces more rapid behavioral changes
than does Ritalin, it is accompanied by side effects of increased
severity, e.g., anorexia, insomnia, and gastric upset.

Benzedrine is the parent compound from which Dexedrine was
refined. As such, it too is a psychomotor stimulant and produces
the same effect as Dexedrine, however it does so at a higher dosage
level due to the presence of the levo-isomer. The Physicians' Desk
Reference (PDR) (1973) advises against the use of either Benzedrine
or Dexedrine in children under three years of age. It recommends a
starting dosage of 2.5 mg. daily in children three to five years of
age. This dosage may be increased on a weekly basis by the same
amount (2.5 mg.) until the optimal response-dosage level for the
individual child is attained. In children older than six, the
starting dosage is 5 mg. daily with weekly increases of the same
amount (5 mg.) until the optimal response-dosage level is attained.
The average daily dose may range from 5 to 40 mg. per day to achieve
the desired result, i.e., that level of functioning at which the
effect of the chemical agent is to facilitate the discrimination of
incoming stimuli to the extent that a marked improvement in the
specified aspects of the child's behavior occurs. As with
Benzedrine, Dexedrine is recommended as a form of adjunctive therapy
to the child's individual management and therapeutic program.

The same recommendation is made by the PDR (1973) for Ritalin
hydrochloride (methylphenidate hydrochloride). Ritalin is described
as being a mild stimulant and antidepressant which brightens mood
and improves performance over a variety of situations, such as
school and home behavior as well as performance of academic tasks.
As part of the drug's description, the PDR makes an important point
under the heading of "Special Diagnostic Considerations":

"Specific etiology of minimal brain dysfunction (MBD) is
unknown, and there is no single diagnostic test. Adequate
diagnosis requires the use of not only medical but of
special psychological, educational, and social resources.
The characteristic signs most often observed are chronic
history of short attention span, distractibility, emotional
lability, and moderate to severe hyperactivity; specific
learning disabilities; perceptual-motor impairment, minor
neurological signs and abnormal EEG. The diagnosis of
MBD must be based on a complete history and evaluation of
the child and not solely on the presence of one or more of
these signs. Drug treatment is not indicated for all
children with MBD. Appropriate educational placement is
essential and psychological or social intervention may be
necessary. When remedial measures alone are insufficient,
the decision to prescribe stimulants will depend on the
physician's assessment of the chronicity and severity of
the child's problems (p. 682)."

After the diagnosis of MBD, currently considered the same as
hyperkinetic impulse disorder, is made, it is recommended to start
medication with small doses, e.g., 5 mg. twice a day (b.i.d.), with
gradual increments of 5 to 10 mg. weekly. Daily dosage above 60 mg.
is not recommended. If improvement is not noted after a one-month
period of dosage adjustment to obtain the child's optimal response-dosage level, the drug should be discontinued. Drug treatment should not and need not be continued indefinitely and it may usually be discontinued after the child has reached puberty.

Ritalin is the drug of choice (Millichap & Fowler, 1967) when used in a clinical setting because it produces much less sympathomimetic activity, side effects, than do the amphetamines. The action of Ritalin has been reported by a number of researchers (Natenshon, 1956; Siegler, 1962; Landman, 1958) to be a mild, leveling type of stimulation of four or five hours in duration. It is relatively free of the excessive high and low, peaking and let down, effects of amphetamine action, and consequently affords a longer period of consistent and dependable stimulation to the child.
LITERATURE REVIEW

The majority of researchers involved in evaluating the effectiveness of central nervous system stimulants have reported improvement during the drug phase of their respective studies (e.g., Bradley, 1937, 1940, 1950; Zimmerman, 1958; Eisenberg, 1963; Zrull, 1963, 1964; Connors, 1963, 1964, 1966, 1970; Weiss, 1968; Sykes, 1971, 1972). These improvements have included everything from the researcher's opinion concerning a global behavior improvement to precise, statistically significant, pre-test, post-test findings. Research in this area has been hindered by several factors: Use of sample groups which are non-representative of the hyperkinetic behavior syndrome; very small sample group size; use of global concepts to measure improvement under the drug administration phase of the studies; inadequate control methods within the individual studies; lack of comprehensive individual profiles on each subject in order to determine if the drug used does have some type of effect which is not readily observable. Grant (1962) offers other research design deficiencies for consideration in his review of psychotropic drugs other than CNS stimulants.

Bradley (1937) reported statistically inconclusive results from a study involving the use of amphetamine sulfate, Benzedrine. His subjects (30) were residential patients in an institution for emotionally disturbed children, age range from 5 - 14 years old and of normal intelligence. The presented behavioral problems were...
varied from educational disabilities, with disturbed school behavior, to withdrawn schizoids, and aggressive epileptic children. Information of the actual research design used is vague as is the specific data obtained. His findings after the administration of Benzedrine were: an improvement in school activities; a drive to accomplish; improved speed and accuracy of performance. Generally, observed outside the school setting were decreased impulsivity, mood-swings, and aggressivity. Some decrease in motor activity was usually noted in children who became "emotionally subdued".

While the data collected are reported in vague and generalized terms, the long-range implications involved in it are most important simply because they initiated interest in this area of child disorders and indicated that various aspects of drug effect were in need of much more research. More specifically, the observation that, while all children benefitted from amphetamine therapy, not all benefitted in like manner served to demonstrate that a sweeping generalization regarding a drug's effectiveness as a blanket therapeutic approach with children was unfounded. Also of interest was the finding that in eleven of the twenty subjects who had been given an electroencephalogram (EEG) as part of their clinical evaluation, definite abnormalities indicative of petit mal epilepsy were noted. These "slow waves/seizure waves" appear in other conditions in which awareness is impaired and suggest some type of "cortical impairment". Other researchers, such as Connors (1971) found variations such as these; Werry (1972), on the other hand, failed to note any difference in frequency of EEG abnormalities between normal, neurotic, and
hyperkinetic sample groups. Consequently, Bradley postulated that central nervous system stimulants tend to "arouse this cortical activity and alleviate any behavioral disorders resulting therefrom."

He also noted that there was little correlation between the child's response to Benzedrine and other characteristics, such as age, sex, past behavioral history, or physical condition. This is in reference to the fact previously mentioned that despite the general effectiveness of the drug, certain children who normally would have benefitted did not do so. Finally, Bradley strongly suggested that since the variables involved in a child's behavior are so complexly related and varied, only physicians trained in child psychiatry are capable of competently evaluating and diagnosing them.

Bradley (1940) used a sample group of twenty-one children, nine to thirteen years old, and of normal intelligence (90 - 110) to evaluate the effects of Benzedrine on intelligence. Drug dosage was determined by individual tolerance and averaged 10 - 20 mg. per day. Both forms L and M of the Stanford Binet Intelligence Scale were used in the evaluation. Form L was administered during the drug phase of the study, while form M was administered after drug usage had been discontinued. Various psychomotor tests, e.g., speed and accuracy of mirror tracing, along with an evaluation of changes in reaction time to visual stimuli, were also employed. These tests were administered twice without medication, before and after the drug phase, and once with the drug.

He found that there was no significant improvement for the sample group as a whole in terms of increased intellectual function-
ing while using Benzedrine. Only six children showed changes of ten to thirteen points; three improved while three showed reductions in scores. There was no correlation between the drug effects and age, sex, past history. The general conclusion which Bradley reached was that improvement in school related tasks, which are the best indicators of current intellectual functioning in relation to peers, was not the result of overt increase in intelligence. Benzedrine was reported to have no effect on performance in the psychomotor tests.

In general, when intellectual functioning is increased, as measured by an increase in intelligence quotient, it is due to an improved emotional attitude toward the intellectual task.

Bradley noted the individual differences in drug effect in regard to intellectual functioning; however, he could not offer any explanation as to why this phenomenon occurred. If his research design had been more precise, an explanation may have been possible. The study suffered from several serious deficiencies: The use of too small a sample group drawn from too heterogeneous a population; failure to use a control group; experimenter bias since both he and the staff of the residential institution knew which of the children were included in the study and when they were receiving medication; the attitude of the children may well have added another variable which could have clouded the effects of the drug on specific behaviors, since they all knew that they were included in some type of a study; and, finally, there was a failure to define specific, quantifiable target behaviors to be attained.

In his 1950 study, Bradley summarized his findings to date.
with Benzedrine and dextroamphetamine. With a combined sample group of 288 children, exhibiting the symptomatic behaviors of a number of diagnoses, he stated: "...60 - 75% showed symptomatic improvement, 15 - 25% showed no change, 10 - 15% showed unfavorable responses" (p. 34). He again noted the individual differences in terms of drug effect and contended that while many of the subjects showed drastic improvement in school performance, this improvement was not reflected in their intelligence quotients measured by the Stanford Binet Intelligence Scale. It appears that he was looking for a reliable correlation of improvement in the same subject on both measures, short term school performance and I.Q. scores. However, due to the brevity of his studies and the lack of adequate measures of specific effects, this correlation could never be achieved.

Zimmerman (1958) reported the results of a study which compared methyl-phenidylacetate (Ritalin) to Reserpine. Reserpine is a tranquilizing agent which has been found useful in stabilization of emotions which have been temporarily upset by some stressful situation. He used 108 subjects in this study, all of whom were non-hospitalized, private patients. Fifty-four patients, average age 15.2 years, received chemotherapy using Ritalin. Eighty percent were free from neurological abnormalities, nine percent had epilepsy, and mongolism constituted the remaining eleven percent of the sample. The remaining fifty-four subjects, average age 14.9 years, were matched by pairs with the Ritalin group for age, sex, intellectual level, diagnosis, and behavior. Data taken over six months revealed that no significant change in verbal intelligence, as measured by either the
Stanford Binet or the Weschler Bellevue Intelligence Scale for Adults dependent upon the subject's chronological age, resulted while under therapy with Ritalin; however, behavioral improvement did occur in approximately two-thirds of this sample group. The behavior evaluated was grouped into five categories: (1) Anxious, tense, insecure; (2) hyperactive, aggressive; (3) withdrawn, shy, quiet; (4) unresponsive, slow, depressed; (5) irritable, excitable. Performance retest results on times tasks, such as block design and picture completion from the WAIS, revealed decreased reaction times for the Ritalin group.

The conclusion which Zimmerman reached were: First, that considerable differences in the specific actions of the two drugs did exist, but that the cause was unable to be determined by this study. For example, in behavior defined as unresponsive, slow, depressed, the Ritalin group was rated as 75% improved, whereas the Reserpine group was only 20% improved. Secondly, he concluded that areas of overlapping effect also exist. This is best demonstrated in the finding that behavior defined as anxious, tense, insecure was judged as being improved in 65% of the Ritalin group and in 66% of the Reserpine group.

These conclusions and observations are valuable primarily because the problematic behavior was well-defined and grouped and specific data were recorded. While not being a precise evaluation of the drug effects on the behavior in question, the data do much to further the distinction between those behaviors most likely to be affected and not affected by either of the drugs used in this study.
One major criticism of the study is the fact that the lack of statistically significant data may have been the result of too heterogeneous a population. The variables of age, diagnosis, and indications of organic or psychogenic causation need to be accounted for and taken into consideration in the research design. If Zimmerman had limited his study to a more specific age group which exhibited the same operationally defined behavior and then administered the two drugs, his data would have been more indicative of drug effects for that particular group instead of being generally vague.

A point of interest is the finding that "Reserpine gave better action where hyperactive, aggressive, irritable, and excitable behavior was present originally than Ritalin did (p. 325)." Improvement in these areas is defined as simply a decrease in the amount of overt behavior and over-reaction to environmental stimuli. Consequently, the quantity and not the quality of the behavior was attended to. Connors (1971) makes specific note of this aspect of measurement and concludes that central nervous system stimulants actually increase the total amount of overt activity and that it is the quality of this behavior, not that total amount of energy expended, which is changed by these drugs. Various other researchers have noted this distinction in their own studies (Groover, 1972; Weiss, 1968; Keogh, 1971).

Knobel (1959) discussed in depth the specific criteria which must be considered prior to formally delivering a diagnosis of organic or psychogenetic causation in reference to behavioral
problems exhibited by children. He strongly advocated considering the whole person, i.e., his total physical environment and the reaction that his social environment of parents, peers, and educational representatives have to his behavioral problem, so that the most beneficial therapeutic program for the individual child may be formulated. In a similar frame of reference, Knobel (1962) formally addressed himself to psychopharmacology and the hyperkinetic child; however, he also advocated a more exact specification of the symptoms observed in such children. Symptom specification is of major importance in research and treatment with this population due to the fact that there is, as yet, no one causative factor noted. The cause of the disorder may be related to organic or to psychogenic factors, or a combination of both, and effective treatment is dependent upon the diagnosis in each case. Research can only advance toward finding the most effective treatment by step-by-step movement which is based on precise symptom specification. In addition to a complete behavioral profile, Knobel advocates an evaluation including a neurological examination, an EEG record, and psychological testing to better determine the presence of organic involvement. He defines organic hyperactivity as being: "...erratic, without direction or objective. It is almost ceaseless and without change in school, home, or any other social situation...". "The aggressivity and impulsivity are also without goal and apparently senseless." The psychogenic hyperactive child "...shows some direction and intentionality in his aggressivity and impulsivity. Through observation the child may appear to possess the capability to structure and coordinate various
aspects of his behavior depending on what situation and with whom he finds himself (p. 199)". His recommendations for therapy are for an eclectic approach combining psychotherapy and milieu changes (psychogeneticists) and drug therapy (organicists).

Although espousing more stringent specification of symptoms and a multidisciplinary approach, Knobel's study still suffered from at least one major deficit; a control placebo group was not used. Consequently, not only were the data gathered incapable of being unequivocally compared to a non-drug group to empirically substantiate his findings, but the lack of a control group also detracted from the quality of the data, as it could have been used as a starting point in future research. The data gathered added little to the body of knowledge already accumulated.

Despite its shortcomings, Knobel's study did set an example for research methodology by utilizing a more rigid set of criteria in sample group selection. The group was limited to include only those children who clearly demonstrated the symptomatology of the hyperkinetic impulse disorder. It also further specified the group with which the drug effects were to be measured by limiting admission to those children who were not overtly mentally retarded. The criterion in this instance was the I.Q. score of 90 or above, i.e., within the average range and extending up into the superior I.Q. level.

Once again, the observation that within Knobel's sample group there were cases in which the subject did not improve at all or only slightly when (theoretically) every subject should have improved
demonstrates the fact that there were variables operating which were not identified because of lack of specification of target behaviors. Knobel was forced to conclude that "...in addition to the drug itself, there was a constellation of other factors which may have influenced the therapeutic result in specific cases (p. 201)." He considered these factors to be the sole result of various attitudes and emotional states of the child and parents regarding the use of drugs. Other authors, e.g., Lasagna, 1970; Connors, 1964, have expressed a similar belief, that the subject's attitude is an important variable.

In a very similar manner as Clements (1962), Connors (1967) elaborated in detail the purpose of psychological testing, the specific areas which the tests he and others use are purported to measure, and offers suggestions for the management of the hyperkinetic child which emphasizes those deficits identified through the evaluation. Comly (1964) also went into great detail in describing the diagnostic criteria used by physicians in identifying this syndrome, and not only emphasizes the importance of a psychological evaluation, but also a complete social history to substantiate the diagnosis of hyperkinesis. Thus, he too implicitly advocated a multidisciplinary approach to diagnosis.

A significant step forward in terms of research methodology was taken by Connors (1963) in a controlled study on the effects of methylphenidate (Ritalin) on learning in disturbed children. Eighty-one children made up the sample group, mean age 11.9 years. On the basis of I.Q. distribution, derived from the Weschler Intelligence Scale for Children (W.I.S.C.), the children were divided into three
intelligence groups: low (65 - 79); medium (80 - 91); and high (94 - 135). Half of each group was randomly assigned to either the drug or placebo group. Medication, 10 mg. b.i.d. increased to 30 mg. b.i.d. for the last five days of the ten-day study, was administered on a double blind basis; the child received either drug or placebo. An individual behavioral profile was compiled on each child prior to the initiation of treatment. Pre-drug measures included: W.I.S.C., symptom ratings, Children's Manifest Impulsivity Scale (CMAS), General Anxiety Scale for Children (GASC), Impulsivity Scale, and digit-symbol learning tasks. Post-drug measures were: Digit-Letter paired associate learning, symptom ratings, side effects interview, tremorgraph, Porteus Maze and digit-symbol learning. Because of the short duration of the study, there were different measures used in the pre- and post-test due to the possibility of practice effects influencing the data in the case of the W.I.S.C. and the digit-symbol learning tasks. The anxiety scales were not repeated as the intent was to determine if the pre-test level of anxiety did exert any influence upon the results of the various other measures, and re-testing was unnecessary for the information desired.

Prior to treatment no significant differences were noted on anxiety, impulsivity or learning measures for the groups assigned to Ritalin or placebo. Gain scores on the symptom ratings, derived by subtracting pre-treatment weighted scores from post-treatment rating scores, indicated overall significant improvement in the drug group's behavior, e.g., disobedience, demanding, et cetera. Maze and paired associate learning tasks demonstrated better performance by the drug
group. Analysis of the data indicated that there was a significant reduction in the number of errors only in the last block of learning tasks and was more apparent in the children classified as emotionally disturbed. The fact that maze performance scores were significantly better suggests an interaction between the drug and intellectual functioning. Connors (1967) describes the Porteus Maze as being a good non-language estimate of intelligence. Two scores are provided, one being a qualitative estimate of impulsivity and the other being a general test quotient comparable to other intellectual estimates. What Connors (1963) seems to imply is not that the drug, methylphenidate, increased the volume of already existing knowledge; rather, that it decreased the inhibiting factor preventing full utilization of existing knowledge and the ability to capitalize on any natural potential for learning that the child has. Consequently, the reported gains demonstrated by the low and average I.Q. children indicate that intellectual functioning was enhanced by the diminution of the inhibiting factor of impulsivity to a greater degree than for children of high I.Q. levels. The anxiety and impulsivity scores derived from the CMAS, GMAS, and the impulsivity scale were analyzed inconclusively to determine if variance on these initial measures might account for the differences of individual improvement noted in the post-treatment symptom rating scale. It was concluded that they measured aspects of the child's behavior and emotional state which were different from those measured by the post-treatment symptom inventory.

The fact that Connors found data to suggest an interaction
between drug effects and intellectual functioning is contradictory to the findings of Bradley, Zimmerman, and Lytton and Knobel (1958). However, this is not surprising due to the fact that this study amassed an extensive individual profile on each child, measuring those specific behaviors which were presenting symptoms of the disturbance. It also measured in greater detail essential and observable aspects of learning, such as the ability to concentrate and the disrupting influences of perceptual visual-motor problems. Consequently, any drug effect would be immediately and concretely apparent. Evaluation of protocols in the post-treatment phase did indicate large, individual differences in responsiveness to Ritalin, specifically in the symptom ratings returned by the teaching and living area staffs.

A point which is somewhat amazing is that Finnerty (1971) failed to replicate this finding of an interaction of drug effect and intellectual functioning when he used dextroamphetamine. The drug itself cannot be blamed; rather, the disregard of reported progress in specification of criteria for evaluation is at fault. Connors and others to be reviewed utilized a wide variety of pre-treatment measures; Finnerty used only the W.I.S.C., Wide Range Achievement Test, medical examination and a brief psychiatric examination. It would seem that Connors' grouping by I.Q. and Lasagna's (1970) grouping into organic and non-organic samples would have encouraged Finnerty to implement these design techniques, especially as his study measures the same areas as Connors', except that dextroamphetamine rather than methylphenidate is used. However, he did not make
use of them and, as a result, Finnerty's data are vague and at odds with reported findings from more precise evaluations of drug effectiveness.

Zrull (1963, 1964) advocated and utilized a multidisciplinary approach to evaluating the effectiveness of d-amphetamine (Dexedrine) on the hyperkinetic syndrome. In his 1963 study a comparison between d-amphetamine, chlordiazepoxide (Lithium, a mild tranquilizer), and placebo was made. Dexedrine was administered in 5 mg. doses b.i.d. for eight weeks. His sample group consisted of sixteen children, 7 - 14 years old, with a median I.Q. of 98, who were referred due to poor school and home adjustment, with the presenting symptoms of distractibility, impulsivity, hyperactivity, and emotional labidity. A wide range of pre-treatment measures, such as psychiatric examinations, reading test, projective and performance tests, and a medical examination were employed. Further examinations in these areas were conducted every two weeks of the eight-week test period. In reporting the results of the study, only vague ratings of improved, no change, and worse were used. Thus, from the reported results, little substantiated and replicable data are available for others to use in continuing research. All that can be said is that in this study the use of d-amphetamine resulted in the largest percentage of improvement.

His 1964 study was beset by similar vagueness in reporting the obtained results. This study compared d-amphetamine, diazepam (Valium, used to control anxiety, tension, fear, and fatigue), and placebo in a sample group of twenty-one children, 6 - 12 years old,
with a median I.Q. which fell in the average range (90 - 110), with the same presenting symptoms of his 1963 study. Dosage and design, double blind cross-over, were administered and conducted and like manner. The major difference is that in this study he administered all psychological testing to a group of eighteen controlled subjects to determine the existence of practice effects; pre- and post-treatment measures were the same as those utilized previously. Once again d-amphetamine was found most effective in reducing the manifestations of the hyperkinetic syndrome.

It is worth noting that Zrull improved the design of his 1964 study, as compared to the 1963 study, by the use of a control group. However, there is still some question as to the reliability of his findings as they apply to the hyperkinetic syndrome because of the make-up of his sample groups. They contained a wide variety of diagnoses, from organic brain damage to anxiety neurosis and also included borderline psychosis. It is possible that variables intimately related to and characteristic of the specific diagnostic categories were introduced and affected by the drug, which further cloud the issue of determining how the drug affects the behavior of hyperkinetic children. A more homogeneous group as determined by pre-treatment measures could provide a reliable sample group, representative of the hyperkinetic syndrome. Additionally, it would seem that grouping by intelligence, initiated by Connors, would have proved helpful not only for determining the effectiveness of the drug d-amphetamine but also of Valium.

Connors (1964) tested the hypothesis that, if intellectual
level does interact with the drug, then the subjects with the lower level I.Q.'s would be expected to exhibit the greatest amount of improvement on the I.Q. related measures: paired-associate learning and Porteus Maze performance. The I.Q. distributions were divided into three groups (see Connors, 1963, already discussed) with half of each group being randomly assigned to receive Ritalin or matched placebo. Eighty-one 2 age for the drug group of 11.92 and of 11.88 for the subjects of the study. The mean was 87.51, and for the placebo group it was 87.51. Ten days with the initial Ritalin dosage gradually increased to 60 mg. per day. The dosage was maintained for the last five days of the study.

The data obtained indicated that there was a trend for the lower I.Q. subjects to receive more benefit from Ritalin than the placebo group derived from the placebo. However, the pre-treatment measures did not include maze performance, whereas the post-treatment did; consequently, it can only be said that there appeared to be a trend toward I.Q. and drug interaction. Paired-associate learning was not uncontestably proved to be affected by Ritalin, nor was sustained attention to experimenter paced tasks. Although neither of these measures appeared to be affected for the group as a whole, it was noted that lower I.Q. children who had been the most distractible did show evidence of a drug effect by their improved performance on these measures.

Lasagna (1970) noted similar effects on Porteus Maze perform-
ance when dextroamphetamine was administered to the sample group. He divided his sample population into organic and non-organic groups, administered a mean dosage of 15 mg. and 20 mg. per day, respectively, and concluded that the organic group demonstrated greater improvement under medication in terms of planning behavior. However, the qualitative scores of the two groups was not significantly different.

It is of interest to be aware of the distinction between these two studies. Connors' lower I.Q. groups which demonstrated improvement on this measure were cited as having I.Q. scores of low (50 - 79) and medium (80 - 91), indicating that some degree of mental retardation did exist for the majority of the subjects; average I.Q. at that time ranged from 90 - 110. Lasagna's organic group had a mean I.Q. of 98.6, but through a detailed evaluation were determined to have had CNS damage in their history due to sustained fever greater than 106 degrees, cyanosis at birth, and premature delivery. Consequently, not only are those hyperkinetic children who are overtly shown to have brain damage benefitted by CNS stimulants, but also benefitted are those who, while possessing the intellectual capability to score within the average range, still exhibit symptomatic hyperkinetic behavior due to more subtle forms of brain damage. If the I.Q. scores alone were used as an indicator of the most beneficial form of intervention, on the basis of Connors' findings, Lasagna's group would be excluded. Only by means of thorough evaluation of the individual child can naive distinctions, leading possibly to less effective intervention, be eliminated.
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Connors' critique of his own design and data indicates
possible factors which may have influenced the results: Too heterogeneous a sample group which may have included subjects whose major learning problem was not due to distractibility; short duration of the study; too rapid dosage increase; verbal administration of anxiety scales, which may have reduced their validity; motivation due to the patients' attitude regarding the drug and of being included in the study may have had some type of influence.

Eisenberg et al. (1965) found that dextroamphetamine in doses of 10 to 30 mg. per day increased performance on the Porteus Maze at a statistically significant level in hyperkinetic children in the lowest I.Q. range of his sample (65 - 79). He attributes this improved performance to a decrease in impulsivity which allowed the subjects to utilize their planning ability before going into action.

It is interesting to note that before Ritalin caused an improvement in performance, the dosage had to be raised to 60 mg. per day (Connors, 1964). Dextroamphetamine, however, evidenced a similar improvement at much smaller dosage in Eisenberg's study, i.e., 10 to 30 mg. per day. This difference in dosage effectiveness may account for contradictory or inconclusive data simply because there has been no formal investigation into the effect variation of different levels of medication, except Knobel's (1959) study which provided only global measures of change, such as improved, slightly improved, and not improved.

Sykes (1971) found that Ritalin significantly improved Continuous Performance Test (CPT) results, a test which demands sustained attention of hyperactive children. These subjects are
shown to have detected more significant stimuli than did the children on the placebo. Ritalin apparently helped the hyperactive child to evaluate the stimuli presented more effectively and to inhibit response to non-specific stimuli. Sykes postulated that perhaps the clinically noted restlessness is not due to simple activity, but to a continuous shifting from one task to another due to a short attention span. If so, and if Ritalin improved sustained attention, as this study indicated, these children would present the appearance of being less restless.

Following this track, Sykes (1972) noted that methylphenidate (Ritalin) increased detection of significant stimuli on the CPT and reduced errors, multiple responses, and non-observing behaviors. This increase in the number of significant stimuli noted suggests that Ritalin reduced the incidence of momentary lapses of attention. The specific task stimuli were more accurately identified and appropriately utilized when the children were receiving Ritalin, as demonstrated by a decrease in errors. Impulsive responding and gross inattentiveness to the task were reduced, thus seeming to indicate that restlessness was also reduced simply by being able to attend to the task at hand.

In a similar vein, research on dextroamphetamine has shown that this drug has a beneficial calming effect on hyperkinetic children. However, there are little data to clearly define the behavioral locus of these effects, i.e., global concepts of behavior have been measured without regard to their point of origin nor how that point is affected by the specific drug. Findings, such as the
fact that gross body movements, i.e., overactivity or restlessness, are unaffected while maze performance and paired-associate learning tasks are (Connors, 1963), suggest that the drug may be operating in a more complex fashion. There may be various interpretations, such as that the drug works in ways which are specific to the individual child receiving it, or that what changes is the manner in which the behavior is organized in response to current environmental stimuli. These alternative interpretations hold more research potential than simply claiming that the central nervous system stimulant in question has a calming effect.

Connors (1966) attempted to evaluate the effects of dextro-amphetamine on organized fine motor behavior under mild stress. His subjects were thirty-two children of outpatient status who had been diagnosed as hyperkinetic on the basis of available information from the child's history, physical examination, and observation. All the children had I.Q.'s greater than 80 and were non-psychotic, without signs of gross organic brain damage, and without a history of serious delinquent behavior. The mean age was 9.6 years with a range of 7 - 14 years of age. The study was eight weeks in duration and the dosage of medication was begun at 10 mg. b.i.d. and then increased to attain the individual child's optimal response-dosage level.

Connors' data demonstrated that the greatest amount of benefit from the drug occurred under maximal stress, i.e., having to respond in a certain amount of time and receiving a mild auditory punishment for incorrect responses. In other words, this means that in a visual discrimination task involving some amount of experimenter-induced
stress, i.e., decreasing the time between the presentations of the stimulus slides, the hyperkinetic children performed better, that is, reduced the number of errors, than they did in the same situation prior to treatment. Campbell (1971) noted similar effects with methylphenidate. Also noted was the fact that motor control, as measured by a tremorgraph, was not affected. Consequently, Campbell concluded that there was some differential action of the drug on behavioral functions. In addition to the effects already mentioned, it was noted that school performance and the symptomatological behavior of hyperkinesis were concurrently improved. The fact that fine motor control was not overtly affected may be due to a lack of specification of just what the parameters of fine motor control are. Epstein (1968) noted that dextroamphetamine did significantly improve fine motor coordination in a group of hyperkinetic, organically involved children.

Connors (1966) states that the data are not unequivocal proof of a specific action of the drug Dexedrine. Rather, practice effects and adaptation to a situation may have contributed to the results. Thus, he indicates variables which need to be eliminated or incorporated into the test design in order to make the effects of the drug used more specific, and to identify other variables which might cause the individual differences in responsiveness to the drug.

McConnell et al. (1964) contend that "...hyperkinesis may be an artifact of observation, reflecting more the way activity is channeled relative to social demands than physical energy per se" (p. 649). Therefore, if improvement in areas such as visual
discrimination lends itself to orienting toward more goal-directed tasks, even though the amount of overt behavior is not reduced, the behavior is still possibly considered by an observer to be less random. If the child is able to focus on one task longer and work toward an apparent goal, the behavior then takes on a socially acceptable and environmentally appropriate appearance, thus seeming to be less intense.

In a double-blind study, Weiss (1968) investigated the effects of dextroamphetamine and compared the results of this study to those obtained in a study using chlorpromazine, a tranquilizer, on behavior and intellectual functioning. She concluded that dextroamphetamine reduced hyperactivity relative to distractibility. This reduction resulted in more goal-directed behaviors. Chlorpromazine was found to be more effective, due to its generally consistent tranquilizing action, for the group as a whole; whereas, dextroamphetamine was more variable in its effects on an individual basis for each child. Some children did benefit from its use, while others did not; those who did benefit demonstrated greater improvement than those children who were rated as improved using chlorpromazine.

Cognitive and motor functions were evaluated by obtaining 32 pre- and post-treatment measures derived from five tests: W.I.S.C., Primary Mental Abilities Test (PMAT), Bender Visual-Motor Gestalt Test, and the Lincoln-Oseretsky Motor Development Scale. There were no statistically significant improvements on any of the measures which could be attributed to the action of dextroamphetamine. However, a trend toward significance was noted on the W.I.S.C.-Verbal...
I.Q., vocabulary and digit symbol subtests, and on the PMAT-I.Q.

A major directional change in research in this area was advocated by Weiss: Movement away from global definitions of improvement and toward a more exacting approach, i.e., measuring the drug effect on specific presenting symptoms or target behaviors and determining the interrelatedness of these findings with those related to other symptoms of the syndrome. She also advocated attending to variables which were indicated by previous research to perhaps have some influence on the effectiveness of the drug, e.g., levels of intelligence, diagnostic homogeneity of the sample groups, and placebo effects.

Knights (1969) utilized a sophisticated set of pre- and post-treatment measures which included individual psychological, medical, and behavioral ratings, in evaluating the effects of methylphenidate on motor skills and learning problems. Children receiving Ritalin demonstrated an improved ability to attend to the task at hand which appeared to be the basis for better motor coordination and performance skills. These skills include performance on the W.I.S.C. subtests of coding, block design, and picture completion. In attempting to determine why only certain children's performance or behavior improved, he could not identify any overt characteristics, e.g., age, sex, history, which would permit a reliable prediction to be made as to the drug's effectiveness. Knights suggests that it is a combination of the drug itself and the attitude of the child or parents toward chemotherapy which may determine its effectiveness. Other researchers (Bradley, 1940; Knobel, 1961; Eisenberg, 1963; Connors, 1964) have
suggested this explanation of differential functioning of the drug's effect; however, no one has investigated this individual variable or has provided any empirical evidence that it does have an effect on the response of hyperkinetic children to central nervous system stimulants.

Connors (1970) compared the effectiveness of dextroamphetamine, methylphenidate, and placebo on seventy-one children, average age 9.5 years. They were referred either because of severe behavior problems in the home or school setting or because they were failing academically. No children with known organic brain syndrome, retardation, or medical illness were included in the sample. A detailed behavioral profile was compiled on each child from pre-treatment measures. Data obtained on post-treatment measures revealed few significant differences between the two active drugs, but did reveal that children are differentially affected. The question of why this occurred led to the formulation of the hypothesis that differences between and within studies are due to different kinds of changes in different kinds of patients. Data from studies which were experimentally the same as the current one, and by the same author, were compared and analyzed. Thus, through a detailed analysis of 107 drug-treated and 71 placebo-treated patients, seven distinct natural groups were concretely identified within the sample. These groups are:

**Group I**  This group has a mean age of approximately 9.5 years, has very low eye-motor (E-M) coordination and attention span, achievement, spatial orientation (SO), and parent and teacher rating scores.
**Group II**  Slightly younger than Group I with very low perceptual integration (PI) as measured by the Bender Gestalt, SO, and teacher rating scores. This group also had low attention span, E-M, and cognitive (verbal I.Q.) scores with parent rating scores slightly above the seriously deficient level.

**Group III**  Approximately the same age as Group II, with very low SO; poor cognitive, PI, achievement, and parent rating scores; slightly elevated E-M, attention span, and teacher rating scores.

**Group IV**  Very low achievement, PI; low cognitive, attention span, and teacher ratings; slightly elevated E-M and teacher rating scores; elevated SO highest scored measure. Same age as Group II.

**Group V**  Approximate mean age of 9.5 years with low teacher and parent rating scores; elevated achievement, cognitive, and attention span scores; average scores on PI, SO, and E-M.

**Group VI**  Approximately the same age as Group II, with very poor teacher rating scores; poor achievement scores; average scores on cognitive, attention span, and parent ratings; elevated PI, SO, and E-M.

**Group VII**  Slightly older than mean age, with low cognitive, E-M scores, elevated teacher ratings and PI; slightly elevated achievement, SO, teacher rating, and attention span scores.

Each of these groups was shown to be differentially affected by dextroamphetamine and, when these group descriptions are used, the
predictability of successful improvement in specific areas is greatly enhanced. Group V was the only exception to the finding that the drug improves various components of the child's problem areas. These children, who constituted approximately twenty percent of the sample group, seemed to have been referred because of overconcern on the part of the parents, and possibly because of some active neurotic inhibitions getting in the way of the child's functioning at his optimal level within the classroom. As a result of medication, these groups all improved on one or more of the post-treatment measures.

These findings have led to further questions regarding group differentiation. As it exists now, the grouping is based on behavioral measures. Further investigation is being conducted to determine whether neurophysiological groupings also exist and contribute to the variability in drug effectiveness. In dealing with cortical evoked responses, Connors found limited data to suggest that the grouping procedures based on evoked response latencies and amplitudes are effective in revealing drug-induced differences in behavior which were previously obscured by inadequate sampling procedures. These findings on evoked responses substantiate the concept of grouping according to individual differences in both behavioral and neuro-
physiological aspects.

On another track, Creager (1967) investigated the effects of methylphenidate on the production of speech in children with cerebral dysfunction. Maintaining a dosage level of 40 mg. per day for three days just prior to testing, he found that three major variables (total words, number of responses, and number of incomplete utterances) were statistically demonstrated to have improved under the drug phase of the study. While the results were statistically significant and serve to corroborate findings in adult psychiatric patients (Kerenyi, 1959), the conclusion reached is vague in terms of causation. It is unclear whether Creager attributed an increase in speech production to a primary effect of the drug's physiological action or whether he attributed it to the widely-noted increase in attention which allows the child to assimilate more of the incoming visual and auditory stimuli within a test situation.

In a similar test of drug effect on vocalization, Connors (1969) found that dextroamphetamine significantly improved the drug group ability to respond correctly. These subjects showed definite improvement on the auditory-synthesis test; words which are broken down into phonemic components are verbally presented to the subject and he must then identify them. Connors contends that this test probably measures the ability of the child to attend to stimulus inputs, in this case verbal. This effect of stimulants appears to be further substantiated by Anton (1969).

In a study directed more toward basic physiological and behavioral measures of drug effect, Anton administered dextroamphet-
amine to a group of six severely retarded (I.Q. below 30) boys who were non-ambulatory, non-verbal, and who displayed symptoms of hyperkinesis. During one stage of the study, dextroamphetamine was administered in 10 mg. doses once a day for three weeks, and a marked behavior change was noted in two of the boys. They became more sensitive to stimuli in their surrounding environment; were able to attend to objects presented to them, for longer periods of time; were less random in their movements, and showed an increase in vocalizations.

This study demonstrated several important research considerations which have evolved through specification of procedures: First, evidence was obtained that, at least for this specific sample, dextroamphetamine exhibited its stimulating effects to a measurable degree only when it was administered on a daily basis for a period of several weeks. No change in the behavioral measures were attained when the drug was administered for a shorter period of time, e.g., two days. Second, long-term studies with specification of target behaviors, both behavioral and physiological, are a necessity to fully evaluate the drug's effects with specific populations of children. Only by becoming increasingly more specific and by building upon the data of previous research will more reliable predictions of drug effects be possible. In addition, this appears to be the only way to isolate the cause, or causes, of hyperkinecity and to find preventative measures to reduce its occurrence, rather than to continually rely on simply corrective measures. Finally, Anton demonstrated that it is necessary to control as many of the intervening
variables, no matter how subtle, as possible. In his study, the subject's food intake excluded those substances which have stimulating action of their own, e.g., coffee and cola beverages. Consequently, any effects noted on the specified behavioral or physiological measures can be ascribed to the effect of the drug under study with a great deal more confidence than if these variables were uncontrolled and did play some part in determining or altering the effect of the drug.

Sprague (1970) utilized a double-blind design to investigate the effects of methylphenidate (Ritalin) and thioridazine (Mellaril, a mild tranquilizer) on reaction time, activity level, one trial learning with a recognition trial test, and classroom behavior. The data gathered indicated that Ritalin increased learning performance, i.e., the number of correct responses, whereas Mellaril decreased learning. Ritalin simultaneously reduced the activity level, such as excessive wiggling, bouncing, and twisting in the seat. In short, Ritalin improved the child's ability to attend to the task at hand. In addition, it improved the quality of the child's behavior as rated by teachers in five specific areas: Isolation-withdrawal, social isolate, on task behavior, teacher-initiated interaction, pupil-initiated interaction, and overall quality of the day.

A point which Sprague makes is that it is possible that differential forgetting may well occur, i.e., being able to learn a response while in the drug phase of the study but, upon retesting at a later date, the response has been forgotten. Drug effect on short and long term memory is recommended as a field of future research.
Denhoff (1971) investigated the usefulness of a questionnaire type rating scale, The Rating Scale for Hyperkinesis, for teacher evaluation of drug effectiveness. The scale used is contended to have adequate reliability and clinical validity in several unpublished studies; however, the specific data necessary for the reader to evaluate the scale are lacking. The behaviors included on the scale are: Activity, attention, impulsiveness, irritability, aggressiveness, and school work.

Using a double-blind cross-over design running for six weeks, dextroamphetamine was administered in 10 mg. doses per day. The results indicate that teachers are able to distinguish hyperkinetic children from others who, while exhibiting a common feature of a learning disability of visual perceptual-motor or language-related origin, differed in the intensity of the behavior defined by the rating scale. In addition, those children identified as hyperkinetic demonstrated statistically significant improvement in the behaviors measured, while those identified as non-hyperkinetic did not show similar improvement.

Denhoff demonstrated that the use of objective behavioral descriptions can speed not only the process of identifying the children representative of the hyperkinetic syndrome, but also the therapeutic intervention, chemotherapy, most likely to be immediately successful with some of the children thus identified.

In an exceptionally well-designed double-blind study, Conrad (1971) evaluated the effects of dextroamphetamine and tutoring on the behavior, school achievement, and test performance of hyperkinetic
children. Behavior was evaluated on the Schenectady Hyperkinetic Scale (SHS) which includes measurements of hyperactivity, distractibility, and perceptual-motor impairment. In order to be included in the study, specific pre-treatment criteria had to be met: "1. A perceptual age of the Bender Gestalt (as scored by the Koppitz norms) which was one year or more below the chronological age of the child. 2. A Frostig Perceptual Quotient (based on scores in fine performance areas; eye-motor coordination, figure-ground, form consistency, position in space, and spatial relations) of 90 or less. 3. Three or more errors on the Bender Gestalt, which Koppitz found significantly more often in brain injured groups. 4. A discrepancy between verbal I.Q. and performance I.Q. on the W.I.S.C. of fifteen or more points. 5. Variability among the subscores on the W.I.S.C. of six points or more. (pp. 46-47)."

Dextroamphetamine treatment was begun at doses of 5 mg. daily and increased by 5 mg. on a weekly basis until the optimal response-dosage level for the individual child had been attained. Most of the 68 subjects reaches a maintenance level of 10 to 20 mg. daily.

Results indicated behavioral improvement, as measured by the SHS, for the dextroamphetamine group but not for the placebo group. Teachers reported even greater improvement in the behavior of those children receiving the drug with tutoring. Performance on perceptual-motor tests also showed improvement. Improved coding scores on the W.I.S.C. was attributed to the effect of the drug, while improvement of the full scale I.Q. was the result of the combined effects of the drug and tutoring. Finally, the effect of dextroamphetamine was to
improve those W.I.S.C. subtest scores most affected by poor concentration, i.e., arithmetic, digit span, picture completion, and coding.

Conrad makes an important point by demonstrating that the perceptual test performance was improved by the use of medication. Consequently, post-medication scores may reveal that a diagnosis of visual-perceptual or perceptual-motor learning disability derived from pre-medication scores may be in error. The individual child's therapeutic program must be constructed on post-medication evaluation in order to attend to the actual problem which the child is experiencing.

Connors (1963), Denhoff (1971), and Conrad all suggest that empirical evidence of total school performance has not been forthcoming due to the normally short duration of the studies focusing on this facet of the hyperkinetic child's behavior. Recommendations for long term studies to evaluate the effects of central nervous system stimulants on school performance have been made as an area of future research.

Campbell (1971), after noting the apparent ease which clinical diagnosticians and researchers interchangeably used labels such as hyperactive, minimal brain dysfunction (MBD), and hyperkinetic to describe what may be clinically separate problems, attempted to add more clarity to the correct usage by specifying the behavioral abnormalities and learning characteristics of a group of children diagnosed as hyperactive. Secondarily, the effect of methylphenidate in alleviating behavioral symptoms was tested to determine if it also facilitated a change in cognitive style and learning problems which
the hyperkinetic child displays. She hypothesized that it might be
the child's specific behavioral excesses, e.g., overactivity, which
undermine his problem-solving ability (cognitive style) and account
for poor school performance.

Four distinct cognitive styles were identified from the
reported search of individuals specializing in this area of cognition
as it relates to developmental patterns of the child. The four style
categories used were: Reflection-impulsivity (R-I) (Kagen et al.,
1964): This category measures the child's cognitive tempo. A
reflective child's tempo is normally long latencies and few errors.
The impulsive child, on the other hand, has short reaction time and
large number of errors and responds immediately without considering
alternative responses which are available to him. Field Dependence-
inddependence (FD-I) (Witkin, 1959; Witkin et al., 1962): The field
dependent child responds globally to the most prominent aspects within
the stimulus field at any given time; whereas, the field inde-
dependent child is able to overcome distracting stimuli and to isolate
specific figures from the ground they are embedded in. Constricted-
flexible control (C-FC) (Klein, 1954; Gardner and Long, 1964): This
category reflects individual differences in ability to ignore dis-
tracting and contradictory cues. The constricted control child cannot
ignore these distractions due to attentional and impulse control
difficulties. Automatization (A) (Broverman et al., 1966; Broverman,
1960): A strong automizer can concentrate on performing simple,
repetitive tasks and do so in a persistent fashion; whereas, a weak
automizer fatigues easily and has difficulty maintaining a rapid
response rate.

In the pre-medication phase, all of the nineteen hyperkinetic subjects could be identified as distinct from the normal control group and demonstrated poorer performance on all measures. The following measures were used as they reflected the styles noted earlier: R-I, Matching Familiar Figures Test; FD-I, The Children's Embedded Figure Test; C-FC, Color Distraction Test; A, Naming Repeated Animals Test and the Color Distraction Test.

The drug phase of the study included eighteen of the subjects from the pre-medication phase plus four who had not been included due to a lack of matched controls. Using a double-blind, own control design, the children were allowed a two-week regulation and stabilization period to adjust to their individual optimal response-dosage levels. Dosage levels at the time of testing ranged from 5 to 50 mg. b.i.d. with a mean of 30 mg. b.i.d. Methylphenidate was effective only in reducing impulsivity on the Matching Familiar Figures Test and in significantly decreasing errors of complete and partial commission on one section of the Color Distraction Test. None of the other measures were significantly altered. The effects of the methylphenidate was to enable the child to become more reflective. Subsequent improvement in achievement, behavior, and problem-solving are attributed to a general increase in attention, response organization, and impulse control. Consequently, in terms of cognitive style, hyperkinetic children are described as being impulsive and field dependent. Campbell entertains the notion that this description is sufficient to explain academic difficulties for some children without
blatantly assuming the presence of specific cognitive deficits, such as impaired visual-motor coordination.

This conclusion is similar to Conrad's (1971) admonition that a child's treatment program be based on post-medication measures to insure that the actual problem, not the one the diagnostician notes on the pre-medication measure and summarily labels as THE problem, is dealt with.

As a result of familiarization with the reported research to date, Arnold (1972) investigated the reported differences in effect which amphetamine sulfate (Benzedrine) and dextroamphetamine have on specific behaviors. Dextroamphetamine, levoamphetamine, and their interaction have been noted in the section on Drugs Selected for Review and will not be commented on here. Arnold hypothesized that it may be possible that a specific behavior is improved by dl-amphetamine because the child is afforded the combined potencies of both isomers. He also hypothesized that, for some children, levoamphetamine (Cydril) may be therapeutically more beneficial than dextroamphetamine because it may be administered at a higher dosage level before the occurrence of the usual amphetamine side effects become inhibiting.

A double-blind cross-over design was used for nine weeks with eleven children, age range from 5½ years to 12 years old, and with I.Q.'s ranging from borderline mental retardation to superior. Assessments of behavior were made by parents, teachers, and clinicians who were unaware of the medication the subject was on at any particular time. The target behavior to be altered was defined
and quantified as possible by the parents, e.g., Billy kicks the wall 80 times a day. The child served as his own control by being exposed to all of the medication phases in the design: Dextroamphetamine, levoamphetamine, and placebo. The dosage levels began at 5 mg. per day and increased by one tablet (5 mg. equivalent) a day until, at the end of the first week, the child took three tablets in the morning and three in the afternoon. After the first week, the individual dosage levels were adjusted up or down to achieve the optimal response dosage level for that particular child.

The results obtained indicated that both dextroamphetamine and Cydrl were significantly more effective than placebo in all measures. In addition, dextroamphetamine was more effective than Cydrl; however, in no case was this difference statistically significant. The measures utilized were classroom behavior evaluated by Connor's (1969) teacher's rating scale, a parent rating scale, the movement toward specified target behaviors, and a clinical rating done by the three psychiatrists involved with the study. In the clinical rating, dextroamphetamine was significantly more effective than Cydrl for the average of the three-week evaluation; however, by the third week of medication exposure to the subjects, Cydrl was no longer significantly different from dextroamphetamine in terms of effectiveness on overt behavior. Dextroamphetamine had more consistent effects than did Cydrl through the three weeks of exposure. Cydrl had gradually increasing beneficial effects until, by the end of the third week, it approximated dextroamphetamine in overall terms of effectiveness.
Two of the eleven children appeared to benefit more from Cydridl than from dextroamphetamine on both the parent and teacher ratings; the target behaviors also showed marked improvement. It was concluded that Cydridl could be more beneficial in treating some hyperkinetic children than dextroamphetamine. Also noted was that by the end of the three-week exposure to each drug, the side effects of insomnia and anorexia were no longer a significant problem. Weight loss was equivalent for both stimulants; however, Cydridl did not cause as many overt complaints. Finally, the target behavior ratings determined by the parents proved to be a very effective and objective method of establishing drug effectiveness and is highly recommended as a standard procedure.

As an outgrowth of his 1972 study, Arnold et al. (1973) re-evaluated the eleven children who comprised the sample group of the previous investigation and assigned them to two different diagnostic groups. What normally would have been two separate groups, over-anxious and hyperkinetic, were combined because so few subjects fell into the overanxious group; only two of the children seemed representative of this category. The final arrangement accounted for all eleven of the children in either the unsocialized-aggressive or overanxious-hyperactive groups. This between-group distinction was advocated by Fish (1971), who contends that differential drug effects on children labeled as hyperkinetic may be due to the existence of different diagnostic categories which better describe the underlying disorder of the individual child, a position similar to that held by Lytton and Knobels (1958). The D.S.M. - II (1968) lists the three
diagnostic categories used by Arnold and described in detail by Fish (1971). These are: 308.1 - Hyperkinetic reaction of childhood (or adolescence) with immaturity, inadequacy, lability, and poor organization; 308.2 - Overanxious reaction to childhood (or adolescence) with nervousness and possible overactivity with subjective distress; otherwise, well-organized behavior; 308.4 - Unsocialized aggressive reaction of childhood (or adolescence), best characterized by aggressiveness and hostility with denial of feelings and personal responsibility; otherwise, well-patterned behavior.

For the unsocialized-aggressive group (5) levoamphetamine (Cydril) was rated as being almost as good as dextroamphetamine on the clinical ratings, i.e., psychiatrist's ratings based on weekly quantification of progress toward target behaviors. The teacher's behavior rating showed that Cydril was slightly better than dextroamphetamine, while the parent's behavior checklist rated both drugs to be of approximate equal benefit.

For the overanxious-hyperkinetic group, Cydril was no more effective than dextroamphetamine on the clinical ratings; and on the teacher's rating, dextroamphetamine was more effective. In general, the results indicate that the aggressive-hostile behavior may be distinct from the hyperkinetic syndrome, even if it is not possible to separate specific symptoms on an all-or-none basis. This behavior is moderated to approximately the same degree by dextroamphetamine or levoamphetamine. However, the overactive and anxious child appears to derive significantly more benefit from dextroamphetamine.

While being hindered in predictive validity as to the adequacy
of grouping according to diagnostic categories and to the eventual usage of levoamphetamine by methodological deficiencies, such as small sample size, retrospective nature of the assignment to groups, and the resultant findings, this study marks a high point in research in this area and possibly in treatment. Admonitions for exactness in design and specification of target behaviors have been made throughout the literature (Knobel, 1961; Fish, 1968; Sykes, 1971). Unfortunately, they were unheeded, and research reports continued to indicate differential drug effects which could not be explained. The behavioral grouping of Connors (1970) is based on pre-treatment test results, but does not place much emphasis on the quality of the interpersonal interactions, i.e., overanxiety, overt aggressivity, et cetera. It may be that quality, in addition to the behavioral specification, which will finally result in a firm diagnosis-treatment approach to this area of childhood disorders. Extensive research must still be carried out in several areas: Research must develop descriptions of individual diagnostic categories which are distinct from other categories based on the severity of the most prominent disorder; must determine the effect which different psychoactive drugs, both stimulants and tranquilizers, have on these categories; must investigate the effects of variation in dosage levels and combinations of drugs on these categories.

Krippner's (1973) research on hyperkinetic children receiving stimulant drugs adds little to the body of empirically-proven effects of the drugs because of design vagueness. The children included in his sample group were diagnosed as hyperkinetic and were either on
medication or had medication prescribed for alleviation of the hyperkinetic symptoms. A series of measures were administered to determine creative thinking ability, I.Q. level from the Peabody Picture Vocabulary Test, and perceptual-motor coordination. Comparison of results of the different measures obtained by the drug and non-drug groups did not differ on tests for cerebral dysfunction, but did on tests for mental ability, creativity, and mental health; the non-drug group did better on all the tests.

Krippner states that most of the children included in the drug group had not been taking their medication during the time the study was conducted; in fact, some of them had never taken the prescribed medication. Consequently, any conclusions he arrived at cannot be anything more than speculation where drug effectiveness or distinction between the groups is concerned. What this study did was to substantiate the fact that children must have a thorough assessment of their individual problems made before they are diagnosed as hyperkinetic. His test results indicated that all children diagnosed as hyperkinetic did, in fact, perform in ways which were detectable on the tests and which distinguished them from the non-drug group. Furthermore, this different behavior was not acceptable to the child's classroom teacher because of its disruptive nature. An important point which Krippner makes is that some schools may currently be trying to maintain the status quo by indiscriminately recommending that children exhibiting overactive (and, therefore, undesirable) behavior be placed on medication. This has been done without first having a thorough evaluation of the child made to determine if
medication is the best remedial course of action. His published study brings out into the open a situation which has only been alluded to previously (Laufer, 1970).

In related research on different modes of intervention, Schnackenberg (1973) conducted a pilot study involving the substitution of caffeine for potentially abuse-prone stimulants, such as Ritalin and Dexedrine. The data obtained indicate that caffeine was just as effective as methylphenidate (Ritalin) with the eleven subjects in the study, as measured by David's Rating Scale for Hyperkinesis. While using Ritalin, the subjects' mean score on the scale was 17.2. During a three-week drug holiday, the scores returned to 25.9; a score of 24 suggests the presence of hyperkinesis. After utilizing caffeine in 200 to 300 mg. doses, taken by ingestion of two cups of regular percolated coffee, the score dropped to 16.8. The coffee was taken both at the morning meal and at the noon meal. In addition to the similar effect upon the behavior of the children, there is the additional benefit of the elimination of undesirable side effects which normally accompany Ritalin and dextroamphetamine, such as insomnia, loss of appetite, nervousness.

It is especially encouraging to note that in describing future research on a more controlled basis, Schnackenberg insists on a rigorous evaluation procedure to be conducted with each child to insure correct diagnosis. He is not advocating the utilization of caffeine as a wonder drug for all children; instead he demonstrates a knowledge of current literature by implying that if Connors' (1970) behavioral groupings could be identified for his sample group, then
the children most likely to obtain optimal therapeutic effects from caffeine would be identified and ultimately benefitted. However, before caffeine becomes an acceptable mode of intervention, it must be thoroughly and extensively evaluated by continued research dealing specifically with the hyperkinetic child, correctly diagnosed as such.
SIDE EFFECTS

The issue of irritating side effects of the central nervous system stimulants has not played a major role in the reported research. The various authors have generally made passing comments concerning the presence and intensity of the unwanted effects and have generally made allowances for a period of adjustment to the particular medication (Campbell, 1971). Knobel (1959) reported individual dosage levels for each of his 63 subjects and the side effects they experienced. His subjects were grouped into six categories: Mild Neurotic (Psychogenic) (P); Severe Neurotic (P); Psychotic (P); Symptomatic (Organic) (O); Neurotic (O); Psychotic (O). He reported no side effects using methylphenidate at dosage levels ranging from 20 to 80 mg. per day for the Neurotic (P) and the Symptomatic (O) groups. The most severely affected group at 10 to 300 mg. per day was the Neurotic (O) group with individual cases of insomnia, anorexia, restlessness, and headache at different dosage levels.

Lytton and Knobel (1958) found it necessary to discontinue use of methylphenidate in only one subject out of 20 at dosage levels of 10 to 200 mg. per day, due to insomnia and anorexia.

Eisenberg (1963) reported a weight loss of an average of 6.8 pounds due to anorexic effect of Dexedrine in his subjects when the dosage level was raised to 30 to 40 mg. per day. Only after this dosage level had been reached did the weight loss occur. Lasagna
(1970) reported an unspecified, but noticeable, weight loss with dextroamphetamine. In addition, he noted that the sample group designated as organic tolerated higher dosage levels per day than did the non-organic group. He hypothesized that this was due to differential excretion levels between the groups. The organic group showed increased urine volume and more rapid excretion of the drug than did the non-organics. He reported the irritating side effects of thirst and a metallic taste in the mouth for one of his subjects. No one else had reported these effects previously. Nine other children were reported to cry without provocation during the first few days on the drug.

Solomons (1971) indicated that if methylphenidate is increased to a greater dosage too rapidly, then there is the increased probability of crying jags, nervousness, palpitations, et cetera. In amphetamines, the sudden increase of dosage or overmedication produces the Panda Syndrome, in which the subject's eyes have dark hollows underneath and he appears pale and pinched. The insomnia and anorexia eventually disappear, but the pale appearance does not.

There is little variation in the nature of the immediate side effects and only rarely can they not be controlled by allowing a period of adaptation and by gradual increases in dosage levels. Arnold (1972) found that by the end of his nine-week study, six weeks of which were under dextro- or levoamphetamine, his subjects ceased to find anorexia or insomnia a problem. He suggests that possibly more has been made of these effects than is actually warranted.
Safer (1973), on the other hand, found that regular intake of stimulant drugs, methylphenidate and Dexedrine, for a period of two or more years, resulted in the inhibition of normal growth in height proportional to the amount of weight suppression over the same period. Dexedrine caused a significantly greater amount of growth suppression than did methylphenidate, and methylphenidate caused suppression only when it was taken in doses of 20 mg. or more per day.

Eisenberg (1971) considers possible side effects from the use of stimulants when he refers to therapeutic orphans, i.e., children who are given stimulants simply in order to quiet them down. He considers a major side effect to be the potential for professionals to side-step the actual problem that is causing the overactivity and to treat only the symptom, not the cause itself.

Barcai (1969) notes a possible side effect as being premature discontinuation of medication due to emerging neurotic family patterns. As long as the child is exhibiting behavior which society labels as bad, i.e., disruptive classroom behavior, aggressiveness, et cetera, then the problem is the child's. However, when medication eliminates these bad behaviors and the child begins to exhibit a different set of behaviors which is more neurotic in appearance, then the child is sick and the problem becomes his parents'. If the parents and other members of the family are unable to cope with overt evidence of their neurotic pattern of interaction, the medication is discontinued. It is easier for them to accept a bad child than a sick child who is a symptom of the family's affliction.
Epstein, Harrington, Meagher, Rowlands, Simons (1968) contend that there is no such thing as an innocent drug. When it is introduced into the body, changes occur in accordance to what the drug is designed to do. Simultaneously, other changes may occur which can be as undesirable as the behavior, e.g., infection, over-activity, or aggressivity. To minimize the unwanted side effects, careful evaluation must be made of individual tolerance levels to the drug and of the diagnosis of what it is the drug is supposed to moderate or alleviate.
CONCLUSIONS

1. It is apparent from the literature that researchers have oversimplified and overgeneralized the category of hyperkinetic reaction of childhood to include those nosological categories characterized by organic impairment. Minimal brain dysfunction (MBD), to which the hyperkinetic reaction is sometimes equated, is not a single category; rather, it may cut across several different diagnostic categories and exhibit symptoms of each. The current lack of distinction between labels, i.e., hyperactive, hyperkinetic reaction, MBD, and cerebral dysfunction, tends to leave the impression that all hyperkinetic reactions of childhood are organically determined, i.e., all organically damaged children are hyperkinetic. This has led to the popular notion that all children labeled as hyperkinetic will benefit from central nervous system stimulants (Fish, 1971), whereas, in fact, this assumption has proved to be incorrect (Weiss, 1968; Fish, 1968; Connors, 1970).

2. The literature dealing specifically with the effects of the reviewed central nervous system stimulants on the symptoms of the hyperkinetic behavior syndrome is limited and, until recently, plagued by the following: Uncontrolled experimental design (Bradley, 1940; Zrull, 1963; Krippner, 1973); inappropriate sample composition (Zrull, 1963, 1964; Knobel, 1962); lack
of specification of target behaviors; and a seemingly total disregard for direction evolved in the literature, except for a few researchers, such as Connors, 1970; Fish, 1968, 1971; Sykes, 1971; Epstein, 1968; Arnold, 1972, 1973.

3. There has been enough preliminary search done and sophistication in design achieved so that relevant investigations into diagnostic-treatment refinements of chemotherapy must now be undertaken. This may be done by eliminating the redundant research (Finnerty, 1971) on global measures of improvements in attention span, impulsivity, hyperactivity, et cetera, and by attempting instead to specify whether the underlying disorder of the individual child is psychogenic or organic. More investigations must be initiated to determine which form of intervention is most beneficial to the child thus identified.

4. In view of the findings, it appears that grouping according to behavioral measures is legitimate (Connors, 1970). To date, this approach is the most productive one for isolating and identifying those facets of a child's behavior which are specifically affected by the stimulant. In addition, this grouping serves to further identify categories of children within the total group, loosely referred to as hyperkinetic, who are differentially affected by the drugs. When considered in conjunction with Fish's (1971) admonitions to attend to the underlying disorder, this approach means a return to strict
assessment procedures to assign individuals to specific diagnostic categories, instead of having one conglomerate category referred to as minimal brain dysfunction.

5. A few studies which have proceeded in this manner, e.g., Arnold (1972, 1973), have demonstrated significant gains in understanding not only which children are most adequately described by the existing categories, but also which central nervous system stimulant exerts the most beneficial effect on them.

6. There are ethical implications for researchers, physicians, psychologists, and all concerned with the use of psychoactive drugs with children. As Krippner's (1973) study showed, there are those individuals who, because of their own inadequacies in coping with active children, advocate placement on a chemical agent to calm the child down. The 1971 Conference Report on The Use of Stimulant Drugs in Treating Hyperactive Children states that the aim of chemotherapy is not to solve problems with drugs, but to allow the child to be able to fully interact with his environment to whatever extent he is capable. The final and most important admonition, to professionals, is that any special, co-existing dysfunction, such as perceptual impairment or learning disabilities of other types, must not be left uncared for simply because psychoactive drugs are available and sometimes helpful. The ease of becoming dependent on central nervous system.
stimulants to control overactivity and impulsivity could lead to a lessening of efforts to eradicate the actual cause (Eisenberg, 1971).


Fish, B. The one child, one drug myth of stimulants in hyperkinesis. *Archives of General Psychiatry, 1971, 25, 193-203.*


