Effect of long-term treatment of hyperactive children with methylphenidate

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Summary: Three groups of hyperactive children were compared by various measures of outcome 5 years after initial evaluation: 24 who were treated with methylphenidate for 3 to 5 years during the follow-up period, 22 treated with chlorpromazine for 18 months to 5 years, and 20 who had received no medication during the follow-up period. The three groups were matched with respect to age, IQ, socioeconomic class and sex.

No statistically significant differences were found between the three groups on the following measures of outcome: emotional adjustment, delinquency, Wechsler Intelligence Scale for Children, Bender gestalt visual-motor test and academic performance (as measured by number of grades failed).

Initially there was a significant difference between the three groups on ratings of hyperactivity and family diagnosis. Hyperactivity scores decreased significantly over the 5 years; family diagnosis ratings changed little. Analysis of covariance for these two measures showed no difference in degree of improvement between the three groups. Our impression was that methylphenidate was helpful in making hyperactive children more manageable at home and at school, but did not significantly affect their outcome after 5 years of treatment.

Résumé: *Effet d'un traitement à long terme d'enfants hyperactifs au moyen de méthylphénidate*

Chez trois groupes d'enfants hyperactifs nous avons évalué d'après divers critères les résultats d'un traitement cinq ans après la première estimation de ces enfants: 24 enfants ont été traités par le méthylphénidate pendant 3 à 5 ans, 22 autres par la chlorpromazine pendant une période variant de 18 mois à 5 ans, et 20 n'ont reçu aucune médication. Les trois groupes étudiés ont été rangés dans des catégories tenant compte de l'âge, du quotient intellectuel, de la classe socioéconomique et du sexe.

En se basant sur les critères suivants d'évaluation des résultats on n'a noté aucune différence entre les trois groupes: adaptation émotive, délinquance, échelle d'intelligence de Wechsler pour les enfants, test visuomoteur à gestalt de Bender et résultats académiques (évalués par le nombre d'échecs scolaires).

Au début, on notait des différences considérables entre les trois groupes concernant l'hyperactivité et le diagnostic familial. L'hyperactivité avait diminué considérablement pendant les 5 années. Par contre, le diagnostic familial n'avait guère changé. L'analyse de la covariance pour ces deux critères ne montrait aucune différence dans le degré de l'amélioration chez les trois groupes. Nous avons l'impression que le méthylphénidate a joué un rôle favorable pour rendre ces enfants plus maniables, tant au foyer qu'à l'école, mais n'a eu aucun effet pourtant sur l'issue globale après 5 ans de traitement.

Over the last 10 years a number of well controlled short-term studies have confirmed the earlier finding of Bradley in 1937[1] that some stimulant drugs are effective in improving both the behaviour, at home and in the classroom, and the school performance of behaviourally disturbed children.[2-6] Some stimulant drugs have been shown to improve performance in laboratory tests of cognitive and motor functions. For example, stimulants were shown to be superior to placebo in tests of sustained attention,[7,8] impulsivity and rote learning,[9] short-term memory,[10] motor skills[11] and cognitive styles.[12] Since all these functions are related to learning and most have been found to be impaired in children with "learning disabilities", it is not surprising that stimulant drugs have been prescribed increasingly for these children.

The diagnosis of "minimal brain dysfunction"[13] has received increasing attention and has been subclassified by Wender[14] into a number of separate syndromes. Included in this broad category are disorders in some schizoid and some psychopathic children, and learning disorders and hyperactivity. Many such children have responded well to stimulant drugs.[14]

Because of the encouraging results from both research studies and clinical practice, stimulant drugs have in the last decade been used with increasing frequency for an ever-widening range of target symptoms in disturbed chil-

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dren. A 1973 survey in greater metropolitan Chicago, in which 700 physicians were polled, indicated that 2 to 4% of school-aged children were treated with psychotropic drugs for an average duration of 9 months.[15]

This increased use of stimulants eventually caused much controversy and concern among professionals and parents, which finally resulted in public outcry in the news media in the late 60s and early 70s. Various professional committees were then set up both in the United States and Canada to study the problem of the use and misuse of stimulant drugs and to answer questions as to their safety, the possibility of addiction, their misuse in overcrowded, understaffed classrooms to subdue the children, and their long-term value.

Under the sponsorship of the US Department of Health, Education and Welfare, a panel of interdisciplinary professionals was set up in 1971 to formulate guidelines for the use of stimulant drugs. The panel, chaired by Dr. Daniel Freedman, concluded that "There is a place for stimulant medications in the treatment of hyperkinetic behavioral disturbance, but these medications are not the only form of effective treatment." The panel suggested that in many crucial areas there was lack of information, and recommended much more careful research; in particular, the need for long-term follow-up studies on the use of stimulants, as to both efficacy and safety, was emphasized.[16]

The present study addressed itself to two main questions: first, whether the prognosis for hyperactive children is improved in those who have taken stimulants, specifically methylphenidate (Ritalin), for many years; and second, whether methylphenidate given in moderate doses under close medical supervision has deleterious effects on growth or cardiac function or both.

Patients and methods

Patient groups

From a total of 150 hyperactive children evaluated in the psychiatry department of The Montreal Children's Hospital between 1962 and 1967 three groups were selected according to medication received — methylphenidate, chlorpromazine or none. All children receiving more than one drug were excluded from the study, as were those who had taken a drug for longer than 4 months but less than 18 months. The children in the three groups were matched with respect to age (at initial evaluation), full-scale IQ (Wechsler Intelligence Scale for Children [WISC]), socioeconomic class (Hollingshead Scale) and sex, and were compared as to outcome 5 years after initial assessment. The mean ages in groups 1 to 3 was 7.96, 8.15 and 8.21, respectively. The mean WISC full-scale IQs were 105.50, 102.27 and 97.90, respectively. The mean socioeconomic class scores were 3.42, 3.32 and 3.45, respectively.

Group 1: This group included 24 hyperactive children initially evaluated in 1967 who had been treated with methylphenidate only for at least 3 years. Twelve were still taking the medication at the time of the 5-year follow-up evaluation, and methylphenidate was discontinued 2 weeks prior to reassessment; in the other 12 the drug had been discontinued within the previous 24 months. Daily dose of methylphenidate varied from a minimum of 20 mg (in two divided doses) to 50 mg (in three divided doses), with one exception, a dose of 80 mg in one child. Average daily dose was 30 mg. (Dose was not calculated on a mg per kg basis because of the varying sensitivity of responsiveness to the drug, which seemed to have little to do with the weight of the child.) Average duration of methylphenidate administration within the group was 51 months.

All children had taken the drug 80% of the time. Most had "drug holidays", usually during school vacations, but also during school time at least once a year to determine if the drug was still effective or necessary or both. Dosage was adjusted periodically at follow-up clinical visits (every 2 to 4 months) in an attempt to achieve at all times maximum therapeutic benefit with minimum side effects. In general, the dose was slightly decreased with increasing age, but in 25% of the group it was slightly increased over the 5-year period. Children were usually weighed and measured three or four times yearly at the follow-up visits.

Group 2: This group comprised 22 hyperactive children initially evaluated between 1962 and 1966, all of whom had been treated with chlorpromazine, 50 to 200 mg daily (mean, 75 mg) in three divided doses, for 18 months to 5 years (average, 30 months). Two children were still receiving chlorpromazine at 5-year follow-up; the medication was discontinued 2 weeks before follow-up evaluation. (Had we made the minimal requirement of 3 years' medication a criterion for inclusion of children in this group, as we did with the methylphenidate group, we would have had too small a number of children. Few took chlorpromazine for even 2 years because both the children and their families preferred the child not to be taking drugs.) During the prescribed period the children took the medication more than 80% of the time. Drug holidays and dosage adjustment followed the principles outlined for the methylphenidate group.

Group 3: This group consisted of 20 children initially evaluated between 1963 and 1966. None had taken medication for longer than 4 months. (In most cases the medication prescribed had been chlorpromazine and the child had been a subject of a short-term drug study.)

Criteria for selection of patients

The 150 children had originally been selected for studies of the etiology of hyperactivity[17] and the effect of various medications on their behaviour and intellectual functioning.[18-20] Criteria for selection were as follows: (a) age, 6 to 12 years at initial evaluation; (b) severe hyperactivity as the main (but not the only) complaint made by both the parents and teachers, and present since their earliest years; and (c) residence at home with at least one parent. Psychotic and epileptic children and those with cerebral palsy were excluded, as were children with IQs below 85 (WISC).

The first short-term study was carried out from 1963 to 1965 with chlorpromazine. At that time stimulants were not being used in our clinic and parents had the choice of chlorpromazine or no drug for their hyperactive children. All the children in the present group 2 and the majority of those in the present group 3 had taken part in the first chlorpromazine study. These children were re-evaluated 5 years later.

Group 1 originally comprised 50 children, all of whom were initially evaluated in 1967 and received methylphenidate as part of a short-term drug study[5] sponsored by Ciba Pharmaceuticals.* None had previously received medication. Of the 50 children 18 had taken methylphenidate for more than 6 months but less than 3 years and were not included in the present study. Statistical analysis indicated that these 18 did not differ significantly from the 26 who had taken the medication for more than 3 years on initial measures of degree of hyperactivity, symptoms on the Peter-Quay symptom checklist, age, WISC full-scale IQ or socioeconomic class. But on the whole they were "poor responders" to stimulants for reasons unknown to us and therefore would have formed a biased control group. Six other children were not traced, and two met the criteria for inclusion in group 1 but their data were discarded from the analysis in order to have the three groups match.

Although one shortcoming of the present study is the

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fact that the patients in group 1 were evaluated initially 1 to 4 years later than those in the other two groups, one of the psychiatrists (G.W.) was present for the evaluation of all three groups of patients, and interobserver reliability studies were carried out for two psychiatrists (K.M. and V.D.[5]) and one psychiatric social worker (E.K.) who later joined the research team and assisted in the evaluations.

Evaluation of outcome

In evaluating the outcome of patients in all three groups 5 years after initial assessment the following measures were used:

Change of hyperactivity scores: Hyperactivity was measured on the Werry-Weiss-Peters "Hyperactivity Scale"[20] at initial and 5-year follow-up evaluations. This rating scale is based on mothers' reports of their children's behaviour during meals, homework, quiet play or working at hobbies, watching television, visiting relatives or friends, and school activities.

Assessment of emotional adjustment: Use of a 3-point rating scale (1 = normal, 3 = severely disturbed) permitted measurement of each of the following factors at 5-year follow-up (poorest possible total score = 21):

1. Peer relations (ranging from popular, to no constant friends, to totally isolated).
2. Mood (ranging from generally in a happy mood, to severe, chronically sad, irritable or angry moods).
3. Sexual adjustment (ranging from age-appropriate, to grossly abnormal behaviour).
4. Relationship with adults, especially parents (ranging from close, warm relationships, to inability to form meaningful ties).
5. Adjustment to authority (ranging from dealing with authority figures well, to rebelling against all authority figures).
6. Number of complaints from mothers at 5-year follow-up (ranging from very few or none, to over 20 complaints).
7. Number of "nervous symptoms" (e.g. phobias, tics, obsessions and hypochondriasis).

Rating of delinquency: Only two children in the three groups showed any delinquent behaviour at initial assessment. Hence, this measure (like "emotional adjustment") was determined at follow-up. Delinquency was measured on a 3-point scale (1 = absence of any delinquent behaviour; 2 = mild delinquent acts without court involvement, such as stealing occasionally from parents; 3 = more serious and more habitual delinquent acts usually with court involvement).

Rating of family diagnosis: This measure was obtained at initial and at 5-year follow-up evaluations. On a 5-point scale each of the following was rated:

1. Number of moves made by the family in the child's lifetime and physical condition of the home.
2. Marital relationship.
3. Psychiatric illness of one or both parents.
4. Continuous presence of mother (or stable mother substitute if mother worked).
5. Deviant child-rearing practices (e.g. overprotection, excessive punishment and extreme inconsistency).
6. Level of anxiety present in family interactions, or "emotional climate" of family.

Assessment of mother–child relationship: This was assessed, by means of a 5-point rating scale, from the impression gained by the psychiatrist or social worker and from the mother's reported evaluation. A score of 1 would indicate a very poor relationship and a score of 5 an excellent relationship.

Mother's impression of change: The mother's impression of overall improvement or deterioration was rated on a 7-point scale, with 7 indicating improvement over the past 5 years to "normal" (just like others his age), and 1 indicating severe general deterioration of behaviour; 4 indicated "no change".

Psychologic tests: The following tests were given to all three groups at initial and 5-year follow-up evaluations:

1. WISC full-scale (verbal and performance) IQ.
2. Bender gestalt visual-motor test.
3. Goodenough draw-a-man test.

In the 12 children still taking methylphenidate at the time of the follow-up evaluation the drug was discontinued 2 weeks before psychologic retesting. The children found it so difficult to concentrate that we decided to repeat the entire testing procedure approximately 5 weeks later, when the 12 children again were receiving medication.

Standard of academic performance: The three groups were compared as to school failure (one or more grades failed) and school success (no grades failed) during the 5 years of follow-up.

In addition, a more elaborate evaluation of school achievement was carried out by comparing the 24 children in group 1 with 37 children whose school performance had been studied extensively by Minde[21] in the years 1969 and 1970. The children in the latter group had been taking a variety of drugs, but none had been on any stimulants for more than 6 months. The children in the two groups were matched with respect to age at follow-up, WISC full-scale IQ, socioeconomic class, sex and degree of hyperactivity at initial assessment. Each child was compared with a classroom control[21] (a normal child in the same classroom, next to the "experimental" child on the alphabetic class list and of the same sex) as to grading of all items on report cards, teachers' rating of conduct items and grades failed. All four groups were then compared. To facilitate comparison the 5-point rating scales used in some report cards were converted to 3-point scales, as used in the majority of report cards. Subjects whose report cards lacked sufficient information were eliminated from the comparison.

Prognostic indicators

Three measures assessed at initial evaluation — degree of hyperactivity, WISC full-scale IQ and family diagnosis ratings — were correlated with four measures of outcome (emotional adjustment, delinquency, mother's impression of change and academic performance) in each of the three groups to determine prognostic significance of these measures.

Physiological assessment

The children in group 1 only were assessed by means of the following studies:

1. Electroencephalography: EEGs were obtained in 22 children in group 1 at initial and 5-year follow-up evaluations. Those 12 children who were still taking methylphenidate at follow-up had EEGs taken while both off and on the drug.
2. Electrocardiography: ECGs were obtained in 23 children in group 1. They were recorded 15 minutes after a rest period while the children were seated. Methylphenidate had been discontinued in each instance at least 14 days before the ECGs were recorded.
3. Repeated measurement of height and weight: Measurements of all 24 children were charted on standard growth curves. Height and weight were measured by the psychiatrist during outpatient visits for dosage adjustment over the 5-year period. For 16 children we were able to obtain from office or hospital charts several readings for height and weight taken before methylphenidate therapy was begun: from these data one of the senior physicians (Dr. D. A. Hillman) predicted the heights at 5-year follow-up evaluation.

Table I—Mean scores (and SDs) for family diagnosis and hyperactivity

Variable	Initial evaluation*			Follow-up evaluation		
	Group 1 (n = 24)	Group 2 (n = 22)	Group 3 (n = 20)	Group 1 (n = 24)	Group 2 (n = 22)	Group 3 (n = 20)
Hyperactivity†	26.02 (3.56)	28.50 (4.96)	30.25 (4.93)	17.25 (5.39)	14.09 (4.71)	15.05 (7.94)
Family diagnosis‡	23.00 (3.55)	19.50 (3.58)	22.40 (5.19)	23.92 (3.93)	20.99 (3.67)	23.20 (4.75)

*Since scores for the three groups differed significantly on measures of hyperactivity and family diagnosis at initial evaluation, these two variable were used as covariates
Hyperactivity: $F = 5.14$; $df = 2,63$; $P < 0.01$.
Family diagnosis: $F = 5.25$; $df = 2,63$; $P < 0.01$.
†Werry-Weiss-Peters "Hyperactivity Scale": maximum possible score, 35.
‡Maximum possible score, signifying best family situation = 30.

Results

There was a significant difference between the three groups with respect to ratings of hyperactivity and family diagnosis, children in group 1 being initially slightly less active and having "better" families (Table I). Therefore these last two measures were used as covariates.

Hyperactivity scores decreased significantly over the 5 years in all three groups ($P < 0.01$) (Table I). Analysis of covariance indicated that there was no difference in the degree of improvement on this measure between the three groups (Table II).

Family diagnosis ratings

These scores changed little over the 5 years (Table I). Analysis of covariance indicated the scores did not differ in degree of change between the three groups (Table II).

Table II—Analysis of covariance of hyperactivity and family diagnosis scores

Source	Adjusted MS*	df	F	P
Hyperactivity				
Between groups	332.68	2	0.38	NS
Within groups	876.21	62		
Total	1208.98	64		
Family diagnosis				
Between groups	276.73	2	0.34	NS
Within groups	822.63	62		
Total	1099.36	64		

*Mean square

Scores of psychiatric variables

Table III indicates that at 5-year follow-up the three groups were not significantly different with respect to emotional adjustment, delinquency, mother–child relationship and mother's impression of change.

Psychologic test scores

There was no difference between the three groups with respect to changes in scores over the 5 years on the WISC full-scale and performance IQ tests, the Bender gestalt visual-motor test and the Goodenough draw-a-man test (Table IV). Since the initial scores on the Bender gestalt test differed significantly between the groups, analysis of covariance was used to assess whether the three groups changed differentially on this measure after 5 years. Table V indicates that there was no difference between the three groups, all scores on the Bender gestalt test improving after 5 years as would be expected. Scores on the WISC (verbal) of children in group 2 were significantly improved after 5 years ($P < 0.05$). Analysis of variance on verbal WISC scores is shown in Table VI. In the 12 children who were tested twice, while receiving and while not receiving medication, there was no significant difference between WISC scores achieved under these two conditions.

Academic performance

Table VII indicates that no statistically significant difference was found in the number of hyperactive children in each of the three groups who had passed each school grade, although there was a trend in group 1 to have a slightly larger number of children who had passed all grades.

Table III—Means (and SDs) and analysis of variance of psychiatric variables in the three comparison groups at 5-year evaluation

Variables*	Mean (and SD)			Analysis of variance		
	Group 1	Group 2	Group 3	F	df	P
Emotional adjustment	10.42 (3.28)	11.45 (2.84)	11.05 (2.33)	0.78	2,63	NS
Delinquency	1.42 (0.65)	1.64 (0.90)	1.30 (0.57)	1.22	2,63	NS
Mother-child relationship	3.00 (1.25)	2.91 (1.48)	3.10 (0.85)	0.13	2,63	NS
Mother's impression of change	5.46 (1.18)	5.27 (1.16)	5.15 (1.04)	1.54	2,63	NS

*See text ("Evaluation of outcome") for explanation of rating scales.

Table IV—Mean scores on psychologic tests

Variables	Initial			Follow-up		
	Group 1	Group 2	Group 3	Group 1	Group 2	Group 3
Performance WISC	106.54	104.58	97.80	108.25	103.59	100.90
Verbal WISC	103.85	101.14*	99.65	103.13	107.23*	99.25
Full-scale WISC	105.50	102.27	97.90	106.17	106.09	100.10
Bender gestalt visual-motor test	22.75†	27.16†	25.05†	35.92†	33.43†	34.30†
Goodenough draw-a-man test	94.79	91.39	89.77	85.97	88.45	88.05

*Difference significant ($P < 0.05$) for initial and follow-up values (see also Table VI).
†Differences significant ($P < 0.05$) among the three groups (see also Table V).

A comparison of report cards between the three groups was impossible because report cards had not been obtained for children in groups 2 and 3. Instead, the report cards of Minde's "mixed-drug" group of 37 hyperactive children and their matched controls were compared with those of group 1 and their matched controls. A multivariate analysis of the academic and behavioural school data was performed using all four groups. Results indicated that there were no significant differences between the two pairs of matched groups on measures of reading, language, arithmetic, French or spelling. The children in Minde's group did significantly worse on the measure of attention ($P < 0.05$) than those in group 1, but the opposite was true for the measure of "approach to work".

The controls did significantly better than the hyperactive children on reading ($P < 0.001$), language ($P < 0.001$), arithmetic ($P < 0.001$), French ($P < 0.05$) and spelling ($P < 0.001$). They also did significantly better on measures of attention ($P < 0.001$), restlessness ($P < 0.001$), concentration ($P < 0.001$) and approach to work ($P < 0.001$). There was no significant interaction effect.

Value of prognostic indicators

In all three groups the WISC full-scale IQ correlated significantly with academic performance. Initial ratings of hyperactivity had a variable and unpredictable relation to outcome measures. Family diagnosis failed to predict outcome on any measure in both group 3 and group 2. In group 1, however, a good family situation was significantly correlated with good outcome as measured by academic achievement, absence of delinquency and emotional adjustment.

Physiological findings

Electroencephalography: In five children the 5-year follow-up EEG was judged to be normal, but the initial EEG had been judged as abnormal. In three other children the follow-up EEG was abnormal, but the initial EEG had been judged normal. Initially 7 EEGs were considered normal and 15 abnormal (epileptiform in 3, multiple diffuse dysrhythmia in 7, centrencephalic in 5 and focal in 1). At 5-year follow-up 9 EEGs were considered normal and 13 abnormal (epileptiform in 4, multiple diffuse dysrhythmia in 6, centrecephalic in 4 and focal in 3). (Some children had more than one EEG abnormality.)

Electrocardiography: None of the ECGs were judged abnormal. The average heart rate was 78 beats/min and the range 64 to 83, except for one child, whose rate was 100 beats/min. Five of the 23 children had "sinus arrhythmia"; this proportion was considered usual by the cardiologist (Dr. J. E. Gibbons). The ECG was also recorded 2 hours after ingestion of methylphenidate by three of the children. No changes in heart rate were observed, so the procedure was not repeated in the other nine children.

Height and weight: Data on height are set forth in Table VIII. Among the 12 children whose methylphenidate was discontinued some time within 24 months before their 5-year follow-up evaluation, the growth curve in 8 increased after methylphenidate was discontinued and in only 3 did the growth curve remain the same. (One child's growth curve was discarded because there were too few readings on it.) No statistical analyses were done on the growth curves because results had not been obtained by a careful experimental method. In addition, no data from an untreated comparison group of hyperactive children were available.

Table V—Analysis of covariance of Bender gestalt visual-motor scores at 5-year evaluation

Source	Adjusted MS	df	F	P
Between groups	598.48	2	0.78	NS
Within groups	769.93	62		
Total	1368.41	64		

Table VI—Analysis of variance on verbal WISC scores

	MS	df	F
Group	692.39	2	2.20
Time	0.67	1	0.02
Group x time†	156.65	2	3.66*

*$P < 0.05$
†Interaction factor

Table VII—Number of children in each group passing all grades or failing one or more grades

Group	No. of children who had never failed	No. of children who had failed
Group 1 (n = 24)	13	11
Group 2 (n = 22)	9	12
Group 3 (n = 20)	6	14

$\chi^2 = 2.592$, df = 2, $P > 0.05$

Discussion

The findings of this study were surprising. All of us had in general been impressed by the efficacy of stimulants for hyperactive children, and we probably all expected the study to demonstrate a better outcome in the children who had received methylphenidate than in those who received chlorpromazine or no drugs. Chlorpromazine had previously been demonstrated in a short-term study[18] to be effective in decreasing hyperactivity (as rated by mothers) but ineffective in improving cognitive functions.

Our failure to demonstrate a better 5-year outcome in adolescence in the children who had received methylphenidate for 3 to 5 years than in children treated with chlorpromazine or not treated at all is difficult to explain, because methylphenidate has proved itself efficacious in several short-term drug studies and in clinical practice.

Possibly when methylphenidate is given for 3 years or longer it becomes increasingly less effective and "tolerance" slowly develops. With some target symptoms (e.g. lowered tolerance to frustration, a crucial personality variable) tolerance to methylphenidate could possibly develop faster that than it does with others (e.g. sustained attention). It is also possible that certain personality variables (e.g. failure to delay immediate gratification and thus to be able to have

Table VIII—Relationship of height and methylphenidate therapy

Child	Difference between observed and predicted heights (cm)	Discrepancy in age for height (mo)	Duration of drug therapy (mo)	Average daily dose (mg)
1	−6	−22	56	50
2	−4	−14	50	20
3	−2½	−13	60	30
4	−7	−13	60	40
5	−6	−12	60	60
6	−6	−9	60	30
7	−4	−8	40	30
8	−5	−8	60	20
9	−2	−2	48	30
10	+2	+10	40	30
11	+2	+2	38	20
12	None	None	60	30
13	None	None	44	80
14	None	None	36	30
15	None	None	60	50
16	None	None	56	30

long-range goals) associated with many hyperactive children do not respond to methylphenidate.

Nevertheless, that tolerance to the therapeutic effects of methylphenidate was the sole or even the main explanation of our disappointing results seems unlikely. Twelve of the 24 children were still taking methylphenidate at 5-year follow-up and the drug was discontinued for 2 weeks before that evaluation. As soon as medication was discontinued we received complaints from nearly all of the teachers of these children (many of whom had not known that the children were previously on medication). Most parents also found those 2 weeks very difficult, but the children on the whole preferred being without "the pills". It seemed clear that methylphenidate was still having an effect on the children at home and at school, making them more manageable in both situations.

A second explanation is that our three groups were not initially equivalent and thus not comparable. One possible objection is the possibility of bias in the group of children receiving chlorpromazine and in the group of children who received no drugs towards the inclusion of less severely disturbed children, because those with more severe problems would have been given stimulant drugs (i.e. more effective medication) by another physician if they had not been prescribed by us for research reasons. But this was not the case with those receiving chlorpromazine. Of the 37 children originally treated with chlorpromazine in a short-term drug study between 1962 and 1966, 1 was lost to follow-up, but the other 36 remained under our observation and all other treatments they received, such as remedial education or family therapy, were known to us. All their medications were prescribed only by us. Stimulants were prescribed by one of us for one child, who was excluded from the present comparison for this reason. Another 10 children were excluded from the present chlorpromazine group because they had received chlorpromazine (only) for less than 18 months, leaving a total of 25 children (3 of these children were excluded in order to match the three groups). By the time we began to favour the use of stimulants for hyperactive children in our clinic (in 1966) the members of the original chlorpromazine group were too old (in adolescence) to begin such treatment.

Two measures at initial evaluation favoured the children in the methylphenidate group: they had significantly "better" families (on the family diagnosis scale) and had lower levels of activity (as measured by their mothers). In contrast, however, scores on the Bender gestalt visual-motor test were initially lower in this group, suggesting that the visual-motor problems were somewhat more severe. This indicates the difficulties of perfectly matching relatively small human groups on many measures, but nevertheless there was no deliberate bias in group selection that would invalidate the comparisons.

A third possible explanation for our results is that the measures we used to assess outcome were too insensitive to detect subtle but important differences between the groups. Delinquency, emotional adjustment and grades failed are very gross measures. Even our family rating scale would fail to detect, for example, better adjustment in the siblings of the treated children, or improved self-esteem in the hyperactive children when this is not reflected directly in better peer relationships, etc. Certainly our measures would fail to detect a variety of possible changes in children, the measurement of which would be difficult. Judging school achievement by number of grades failed is a highly crude method of assessment. Unfortunately even report cards are unreliable. Perhaps academic achievement, unless dramatically affected by a treatment method, is best assessed under laboratory conditions.

It is possible that the hyperactivity rating, which relied on the mother's assessment, was biased against the children who received methylphenidate. It is possible that the parents of the 12 children who had been taking medication until 2 weeks before evaluation overreacted to their child's regression towards more hyperkinetic behaviour, which would be reflected in higher ratings on the Werry-Weiss-Peters scale. A longer interval before evaluation would have allowed the parents to become accustomed again to their child's behaviour without medication. This reservation applied only to the hyperactivity rating and not to other measures of behaviour, all of which involved observation over a long period of time (e.g. delinquency).

Regarding the safety of methylphenidate when given for 3 to 5 years in moderate dosage (mean daily dose, 30 mg) with drug holidays, no detrimental effects were observed on the ECGs or EEGs.

Data for growth curves were obtained in a clinical manner without stringent research methodology, and an untreated hyperactive control group was unfortunately lacking. Nevertheless, inspection of the growth curves of those children who took methylphenidate for 3 to 5 years gives some cause for caution and concern. Findings suggest that children who take methylphenidate even in moderate doses for several years may in some cases fail to grow at expected rates. These tentative results, which are in no way considered conclusive, nevertheless confirm the findings of Safer, Allen and Barr.[22] More carefully controlled studies are required before we will have definitive data on the effects of stimulants taken for many years on growth patterns. Until that time it would seem wise to discontinue stimulants in adolescents for a year or two before closure of their epiphyses.

Perhaps our findings can be summarized by suggesting that we initially expected too much from any one drug or from any one method of treatment of hyperactive children. Barbara Fish has aptly entitled one of her papers "The 'one child one drug' myth of stimulants in hyperkinesis".[23] There is no doubt that stimulants are effective drugs for many hyperactive children, but as the sole method of management their value is limited. Although the hyperactive child on stimulants generally becomes easier to handle, his ultimate outcome may be only slightly or not at all affected. An interesting finding in this study is that only among those taking methylphenidate did initial ratings on family diagnosis predict final outcome for almost every measure of outcome; that is, in this group only there was a significant correlation between family diagnosis and school achievement ($P < 0.05$), delinquency ($P < 0.05$) and emotional adjustment ($P < 0.01$). This suggests strongly that there is an interaction between a useful drug and a healthy family that influences the prognosis. Similarly, one can postulate that a useful drug would interact with other treatment variables such as behaviour modification, family counselling, optimal classroom situations and skilled and supportive teachers to change the final outcome. It was wishful thinking on our part that a useful drug alone would change the outcome of a fairly serious condition like severe chronic hyperactivity, with multiple etiologic factors and multiple and various manifestations.

References

1. BRADLEY C: The behaviour of children receiving benzedrine. *Am J Psychiatry* 94: 557, 1937
2. EISENBERG L, LACHMAN R, MOLLING PA, et al: A psychopharmacologic experiment in a training school for delinquent boys. *Am J Orthopsychiatry* 33: 431, 1963
3. CONNERS CK, EISENBERG L: The effects of methylphenidate on symptomatology and learning in disturbed children. *Am J Psychiatry* 120: 458, 1963
4. CONNERS CK, EISENBERG L, BARCAI A: Effect of dextroamphetamine on children: studies on subjects with learning disabilities and school behaviour problems. *Arch Gen Psychiatry* 17: 478, 1967
5. WEISS G, MINDE K, DOUGLAS V, et al: Comparison of the effects of chlorpromazine, dextroamphetamine and methylphenidate on the behaviour and intellectual functioning of hyperactive children. *Can Med Assoc J* 104: 20, 1971
6. DENHOFF E, DAVIS A, HAWKINS R: Effect of dextroamphetamine on hyperkinetic children: a controlled double blind study. *J Learn Disabilities* 4: 27, 1971

7. CONNERS CK, ROTHCHILD G: Drugs and learning in children, in *Learning Disorders*, vol 3, edited by HELMUT J, Seattle, Spec Child, 1968, pp 193-223
8. SYKES DH, DOUGLAS VI, MORGENSTERN G: The effect of methylphenidate (Ritalin) on sustained attention in hyperactive children. *Psychopharmacologia* 25: 262, 1972
9. CONNERS CK, EISENBERG L, SHARPE L: Effect of methylphenidate (Ritalin) on paired associate learning and Porteus maze performance in emotionally disturbed children. *J Consult Psychol* 28: 14, 1964
10. SPRAGUE RL, BARNES KR, WERRY JS: Methylphenidate and thioridazine: learning reaction time, activity, and classroom behaviour in emotionally disturbed children. *Am J Orthopsychiatry* 40: 615, 1970
11. KNIGHTS RM, HINTON GG: The effects of methylphenidate (Ritalin) on the motor skills and behaviour of children with learning problems. *J Nerv Ment Dis* 148: 643, 1969
12. CAMPBELL S, DOUGLAS VI, MORGENSTERN G: Cognitive styles in hyperactive children and the effect of methylphenidate. *J Child Psychol Psychiatry* 12: 55, 1971
13. CLEMENTS SD, PETERS JE: Minimal brain dysfunction in the school age child. *Arch Gen Psychiatry* 6: 185, 1962
14. WENDER P: Minimal brain dysfunction in children. New York, Wiley, 1971
15. SPRAGUE RL, SLEATOR EK: Effect of psychopharmacologic agents on learning disorders. *Pediatr Clin North Am* 20: 719, 1973
16. FREEDMAN D: Report on the conference on the use of stimulant drugs in the treatment of behaviourally disturbed young school children. *Psychopharmacol Bull* 7: 23, 1971
17. WERRY JS, WEISS G, DOUGLAS V: Studies on the hyperactive child. I. Some preliminary findings. *Can Psychiatry Assoc J* 9: 120, 1964
18. Idem: Studies on the hyperactive child. III. The effect of chlorpromazine upon behaviour and learning ability. *J Am Acad Child Psychiatry* 5: 292, 1966
19. WEISS G, WERRY J, MINDE K, et al: Studies on the hyperactive child. V. The effects of dextroamphetamine and chlorpromazine on behaviour and intellectual functioning. *J Child Psychol Psychiatry* 9: 145, 1968
20. WERRY JS: Developmental hyperactivity. *Pediatr Clin North Am* 15: 581, 1968
21. MINDE K, WEBB G, LAVIGUEUR H, et al: The hyperactive child in elementary school: a 5 year controlled follow-up. *Except Child* 38: 215, 1971
22. SAFER D, ALLEN R, BARR E: Depression of growth in hyperactive children on stimulant drugs. *N Engl J Med* 287: 217, 1972
23. FISH B: The "one child one drug" myth of stimulants in hyperkinesis. *Arch Gen Psychiatry* 25: 193, 1971

Retrospect

Industrial medicine

The conspicuous changes which have taken place in medicine in the last two decades have occurred for the greater part in two fields, first in the field of diagnosis, and second in the field of prevention, and in both these fields the development in industrial medicine has been very marked. Indeed in the first field, namely the diagnosis of industrial intoxications, the most astonishing progress is being made. Each year adds to the number of industrial intoxications which can be recognized and differentiated. As in other cases of development in the refinement of diagnosis the great difficulty is how to make this information part and parcel of the everyday working knowledge of the practitioner, so that disease may be recognized in its early stages and steps taken for its prevention. It was therefore a step in the right direction when the Committee on Industrial Medicine of the Ontario Medical Association last year in one of the small bulletins issued to the profession laid down indications for the diagnosis of lead poisoning in its very early stages. We can all remember when as students lead poisoning was discussed, one of the symptoms referred to and on which a great deal of emphasis was laid was wrist-drop. We now recognize that wrist-drop is an exceedingly late manifestation of the disease; that at the time that it develops, the patient has been so seriously poisoned that a long period of treatment is necessary before he can resume his previous avocation. Lead poisoning can now be recognized with assurance at a much earlier stage, and there is little excuse for the attitude of a medical referee who recently refused to consider a case as one of lead poisoning because the patient failed to show wrist-drop.

Chronic benzol poisoning can now also be recognized at an early stage. Given a history of repeated exposure to benzol fumes over a long time and add thereto some feeling of weakness and lassitude, and a white blood count of 5000 or under, a diagnosis of benzol poisoning may fairly be made. Nowhere in Canada at the present moment have we exact information of the incidence of such industrial poisonings. Very frequently when the employee feels that his work is affecting him deleteriously he leaves, and the damage he has already received only becomes obvious at a much later date. When the Massachusetts General Hospital started its industrial clinic prominent physicians and even members of the staff were of the belief that there was no need for such a clinic, inasmuch as there was little industrial disease. The ordinary physician in Boston and even members of the hospital staff hardly looked to the occupation of their patient to throw any light upon obscure symptoms. An experiment lasting five years has led to a complete change in viewpoint. It is recognized that there exists a great deal of industrial intoxication, and that the present and past occupation of patients must continuously be taken ino consideration if an accurate clinical diagnosis is to be made. Canada is not as yet highly industrialized but there is little doubt that in the larger places more attention could with advantage be given to this problem. — Henderson VE: Editorial, Can Med Assoc J *15: 83, 1925*