Am. J. Hum. Genet. 41:701–741, 1987

A Controlled Study of Tourette Syndrome. I. Attention-Deficit Disorder, Learning Disorders, and School Problems

DAVID E. COMINGS* AND BRENDA G. COMINGS†

*Department of Medical Genetics, City of Hope National Medical Center, and †private practice, Duarte, CA

SUMMARY

Tourette syndrome (TS) is a common, hereditary, neurobehavioral disorder of childhood. To determine the frequency of various behavioral manifestations, we have compared 47 random normal controls to 246 patients with TS, 17 with attention-deficit disorder (ADD), and 15 with ADD secondary to a TS gene (ADD 2^0 TS). All subjects were examined prospectively with a 425-item questionnaire based on the Diagnostic Interview Schedule and the Diagnostic and Statistical Manual of Mental Disorders (DSM III). The TS patients were divided into grade 1 (too mild to treat [17.5%]), grade 2 (requiring treatment [58.9%]), and grade 3 (severe [23.6%]). Patients in all three grades of TS were significantly different from controls for DSM III symptoms of inattention, impulsivity, and hyperactivity. Sixty-two percent of TS patients had ADD, compared with 6.3% of controls; and 48.8% had ADD with hyperactivity (ADDH), compared with 4.2% of controls. In the majority of TS patients, the natural history of the disease was to start with ADDH and 2.4 years later develop motor and vocal tics. Among TS patients, 39% had previously received medication for ADDH or behavior problems, compared with 2% of the controls. Although stimulants can occasionally exacerbate tics, there was no evidence that stimulants cause TS and they are often a valuable adjunct to the treatment of TS. It is estimated that 10%–30% of ADDH is due to or associated with the presence of a TS gene. TS patients had a significantly increased frequency of (1) attending classes for the educationally handicapped, (2) placement in classes for the severely emotionally disturbed, (3) attending any special classes, (4) severe test

Received December 10, 1986; revision received April 9, 1987.

Address for correspondence and reprints: Dr. David E. Comings, Department of Medical Genetics, City of Hope National Medical Center, 1500 East Duarte Road, Duarte, CA 91010.

anxiety, (5) stuttering, (6) letter, number, or word reversal, (7) reading very slowly, and (8) poor retention of material read. A reading-problem score (dyslexia) ≥3 was present in 26.8% of TS patients, compared with 4.2% of controls. Number reversal, word reversal, and poor retention were significant even for the TS patients with tics too mild to treat. The multiple ways in which TS impacts school performance, as well as potential remedies, are discussed.

INTRODUCTION

Tourette syndrome (TS) is a common neurobehavioral disorder. Genetic studies indicate that it is due to a single major gene with a gene frequency of .006 (Comings et al. 1984; Devor 1984; Pauls and Leckman 1986). Thus, 1.2% of the population carry the gene and more than half of them express it in some form. As such, it is one of the most common single-gene disorders affecting man. In addition to the motor tics and vocal noises, it is associated with a wide range of other features, including attention-deficit disorder (ADD), learning disorder, stuttering and other speech problems, coprolalia, echolalia, discipline problems, conduct disorder, obsessive-compulsive behavior, panic attacks, phobias, and others (Eldridge et al. 1977; Golden 1978; Shapiro et al. 1978; Nee et al. 1980; Friedhoff and Chase 1982; Cohen et al. 1983; Comings and Comings 1984, 1985, 1987*c*). Despite these features, it is often considered a benign tic disorder and the behavioral manifestations have generally been underemphasized. There has been some controversy as to whether there are any significant behavioral manifestations or a personality constellation in TS patients. In one of the few controlled studies, Shapiro et al. (1978) compared TS patients with other patients in a psychiatric clinic and concluded that there were no unique personality characteristics. However, this study was set in an era when many believed that the symptoms in TS patients were psychogenically caused and Dr. Shapiro's emphasis was to indicate that TS was actually an organic disorder. If TS is associated with a wide range of behavioral manifestations, it would be critical to use a normal control population rather than patients in a psychiatric clinic.

We report here the first extensive study of behavior in TS patients compared with that in controls. This was a prospective study in which all consecutive new TS and ADD patients referred to the clinic were first required to fill out a 425-item questionnaire modeled on the Diagnostic Interview Schedule (Robins et al. 1981) and DSM III (1980). The controls were picked randomly from the children of mothers entering the Genetics Clinic of the City of Hope National Medical Center for amniocentesis.

In this first of a series of papers, we address the following questions: What percentage of TS patients have ADD? Is ADD an integral part of TS? Is the natural history of TS one of initially presenting as ADD and then progressing to TS? If so, what are the time intervals for this progression? Does the administra-

tion of stimulants to patients with ADD due to a *TS* gene hasten the onset of tics? How often does the administration of stimulants to TS patients make the tics worse or better? What percentage of ADD is associated with the presence of a *TS* gene?

In addition to ADD, we also examined the frequency of other learning and school problems. Although the presence of learning disorders is frequently mentioned as an associated feature of TS (Lucas et al. 1967; Golden 1978; Quinn and Thompson 1980; Cohen et al. 1982; Hagin et al. 1982; Parker 1985; Stefl and Rubin 1985), it has rarely been quantitated. All investigators agree that the IQ of TS patients is normal, although performance IQ often averages 2–11 points less than verbal IQ (Shapiro et al. 1978; Hagin et al. 1982; Sutherland et al. 1982; Bornstein et al. 1983).

In a study of 34 TS patients, Shapiro et al. (1973) reported that 76.6% presented evidence of "organic" impairment, as measured by standardized psychological and other tests. In a well-controlled study of 32 TS patients, 31 controls, 48 learning-disabled subjects, and 30 schizophrenics with their own set of 25 controls, Sutherland et al. (1982) found (1) that of the various IQ subscales, only the digit-symbol test, a measure requiring accurate short-term memory, was reliably low and (2) that copying and drawing from memory (Rey Complex Figure) and delayed recall (Wechsler Memory Figures) were significantly impaired in TS patients. When studies are done on a small number of subjects, they tend to be highly biased. For example, the report of Hagin et al. (1982), based on a study of only 10 TS patients that were admittedly better functioning than average, concluded that TS children's "problems are not problems in learning, but rather problems in demonstrating what they know." By contrast, we find that many TS patients have significant impairment in their ability to learn, to read, and to retain information.

METHODS

Subjects

TS.—Characteristics of the Tourette Syndrome Program at the City of Hope National Medical Center have been described elsewhere (Comings and Comings 1984, 1985; Comings et al. 1984). The majority of cases are either self-referred or referred by school districts or the Tourette Syndrome Association. Since <5% are referred by other physicians because of marked severity or prior treatment failure, a bias toward severe, treatment-resistant cases is avoided. The clinic has no age restrictions, and patients range in age from 2 to 75 years. Since patients are seen regardless of ability to pay, all socioeconomic classes were represented. All patients meeting the DSM III criteria for TS were consecutively entered into the study. The first 250 cases have been the subject of prior reports (Comings and Comings 1982, 1984, 1985, 1986, 1987*c;* Comings et al. 1984). The present study is based on the second 246 cases.

ADD.—Since the clinic also accepts cases of any type of learning disorder, we have also been able to enter into the study the results from 32 cases of ADD/ADDH who received the same questionnaire. Approximately half of these (15

cases) had (1) a positive family history of motor and/or vocal tics, or (2) one or two minor motor tics but no vocal tics, or (3) some minor vocal tics but no motor tics. These were classified as ADD secondary to a *TS* gene (ADD 2^0 TS). Those with a negative family history of tics or vocal noises and having no tics or vocal noises themselves were considered pure ADD (ADD).

Controls.—A great deal of care went into obtaining a totally neutral control population. We specifically rejected the idea of (1) using children with any other diseases, (2) entering the hospital for any reason, or (3) using classrooms of children, since such a group would have many potential biases. We could not pick "unaffected" siblings without motor or vocal tics, since our experience with >800 families has indicated that the *TS* gene may be expressed by various behaviors in the absence of tics. The use of other family members as controls will have to await the development of a genetic marker for the *TS* gene.

We needed a group of parents sufficiently motivated to spend sufficient time to complete the extensive questionnaire with a high degree of compliance. The ideal solution was provided in the form of mothers attending the clinic for amniocentesis because of advanced maternal age. They are required to come in twice, first for counseling and then ~2 wk later for the amniocentesis. These mothers often had children in the same age range as TS patients. In taking a pedigree, we asked no questions about the children except to determine their age, sex, and presence or absence of major congenital anomalies. If the mother was willing to participate in the study and had only one child in the age range of 6–18 years, that child was chosen. If there were multiple children within this range, the one closest to age 15 years was chosen. The mother was instructed to fill out the questions directed to her and to have her child fill out the questions directed toward him or her. Occasionally, to obtain some older controls, siblings of the mothers were also chosen. The questionnaire was turned in at the time of the amniocentesis. This process resulted in complete questionnaires on 24 males and 23 females. The compliance rate was 98%.

Diagnosis

The diagnosis of TS was based on the DSM III criteria of (1) onset between 2 and 15 years of age, (2) presence of multiple motor tics, (3) presence of vocal tics, (4) waxing and waning of symptoms, (5) suppressibility of symptoms, and (6) duration of symptoms for >1 year.

The patients with TS were divided into three grades of severity. In grade 1 cases, the motor and vocal tics were too mild to treat; in grade 2 cases, the tics were of sufficient severity to justify treatment; and in grade 3 cases, tics were sufficiently severe to justify treatment and symptoms of any type were causing significant interference in the patient's life. One advantage of this simple division of cases is that it allows the present study to be easily compared with studies having a different mix of grade 1–3 cases. Thus, if the present (or any other) study has any ascertainment biases toward severe or mild cases, the comparison of the frequency of different behaviors in the different grades (rather than comparison of frequency for the total series) will allow comparisons between different studies. We would be happy to make our questionnaire

available to any other investigators wishing to do a comparable study of their patients.

The diagnosis of ADD or ADDH was based on the DSM III criteria. Any available confirmatory records from teachers or previous physicians were utilized.

Questionnaire

All patients and/or their parents were required to fill out a detailed 425-item questionnaire that was in part modeled after either the questions in the Diagnostic Interview Schedule (Robins et al. 1981) or criteria in DSM III (1980) to make diagnoses of many different disorders. Since the structured questionnaire was completed before the patients were seen and before any diagnosis was made, biases due to different types or degrees of questioning after the diagnosis was known were avoided. In addition, the questionnaire was simply filed away for future analysis. Its contents were not used for diagnostic purposes. Diagnoses were based on a semistructured interview and examination given at the time of the first clinic visit. The analysis of the questionnaires was only undertaken after ~250 TS patients had been accumulated in the new series.

Since this series was completed, we have seen an additional 300 TS patients, for a total of >800. In these later patients we now routinely review the questionnaires with the patients and family at the first clinic visit. We are constantly amazed and pleased with how seriously and conscientiously patients and parents work on these questionnaires. Oftentimes if there is a difference of opinion between child and parent, this is noted. In the personal interviews we have consistently validated the accuracy of the answers. The results for these additional patients are similar to those for patients reported in the present series of papers.

The questions relevant to the present paper were as follows:

A. Prior diagnoses.—"Has a physician or any other professional ever made any of the following diagnoses (yes/no?): minimal brain damage; hyperactivity; attention-deficit disorder (ADD) or severely emotionally disturbed (SED)?"

B. ADD and ADDH Scores.—Five different scores were obtained to evaluate the prevalence of ADD symptoms: Inattention, Impulsivity, ADD (Inattention + Impulsivity), Hyperactivity, and ADDH. These scores were based on a subset of the DSM III criteria for ADDH.

In the following, the capitalized word in parentheses is the variable generated and used in the computer analysis and figures. The three requested responses to the questions were as follows: no (0), occasionally (1), and often (2). In the case of children, the parents were asked to answer the questions on the basis of their observations.

For the Inattention score the following five questions were asked: 1. "Do you fail to finish things you start?" (FINISH). 2. "Do you seem not to listen to your parents or teachers?" (LISTEN). 3. "Are you easily distracted?" (DISTR). 4. "Do you have difficulty concentrating in school and elsewhere?" (CONC). 5. "Do you have difficulty sticking with play activities?" (PLAY).

For the Impulsivity score the following five questions were asked: 1. "Do you often act before thinking?" (THINK). 2. "Do you have trouble organizing your work?" (ORG). 3. "Do you need a lot of supervision?" (SUPER). 4. "Do you frequently call out in class?" (CALL). 5. "Do you have difficulty awaiting turn in games or group situations, i.e., are you impatient?" (INPAT). The sixth criterion in the DSM III—"Do you shift excessively from one activity to another?"—was asked but left out of the analysis because the results were (1) essentially identical to those for PLAY (above) and (2) easier to conceptualize with only five variables in each category, to give a maximum score of 10 each for Inattention, Impulsivity, and Hyperactivity.

For the Hyperactivity score the following five questions were asked: 1. "Do you run about or climb on things excessively?" (RUN). 2. "Do you have difficulty sitting still?" (SIT). 3. "Do you have difficulty staying seated?" (SEAT). 4. "Do you move about excessively in your sleep?" (MOVE). 5. "Are you always on the go?" (GO).

C. Age at onset of ADD.—"If many of these things (above) are answered 'often,' at what age did these things first begin?"

D. Age at onset of tics and vocal noises.—"If you had muscle tics, at what age did these first begin? If you had vocal tics, at which age did they first begin?"

E. Prior stimulant medications.—A series of questions were asked regarding prior stimulant medications and their affect on hyperactivity, ability to concentrate, school performance, and tics (see Results).

F. Special classes.—The patients/parents were asked whether they ever had been in the following special classes: educationally handicapped (EH), learning handicapped (LH), learning disabled (LD), and severely emotionally disturbed (SED).

G. Other problems.—Questions were asked concerning the need for a special teacher, the need for a home teacher, and whether they had ever flunked a grade or been advanced a grade.

H. Reading-problem score.—The following six questions were asked regarding reading problems: "Did you ever have frequent problems with any of the following: Letter reversal (p for q, b for d, etc.)? Number reversal? Word reversal (saw for was, etc.)? Drop or insert words while reading aloud? Read very slowly (word by word) when your peers were reading normal speed? Unable to retain the meaning of what you just read?" To obtain a reading-problem scale, each no answer was counted as 0 and each yes answer as 1. These were added, to give a score ranging from 0 (the minimum) to 6 (the maximum).

I. School performance.—To evaluate school performance, the parents or patients were asked, for grades 1–6, is school achievement on the whole below average, average, or above average in the following: math, reading, and writing (spelling and grammar). Where appropriate, the same question was asked for the junior and senior high school patients.

Other questions posed are discussed in the Results section.

RESULTS AND DISCUSSION

General Features

Table 1 summarizes the basic subdivisions of the study population. There were 47 controls, 246 TS patients, 17 ADD patients, and 15 ADD 2^0 TS patients. To determine whether any of the results of the present study might be due to a changing population of TS patients owing to subtle selection of more severe cases, the sex ratio and division into the three grades of severity have been compared to the first 250 cases (Comings and Comings 1985). The sex ratio of this series, 4.0, was virtually identical to that of the first series, 4.1. In addition, the division into the three grades—17.5% grade 1, 58.9% grade 2, and 23.6% grade 3—was also similar to that of the first series—12.4% grade 1, 58.8% grade 2, and 28.8% grade 3 ($\chi^2 = 3.42$; $P = .18$). Thus, there has been no significant change in the character of the TS patients due to changes in referral patterns or selective bias.

The ages of the subjects in the different diagnostic categories are shown in table 2. The mean age of the control group was 19.9 years and that of the TS group 16.9 years. In both groups approximately three-quarters were <21 and one-quarter were >21 years old. The mean ages of these two subgroups were comparable, being 12.8 versus 11.5 years and 37.2 versus 35.9 years. The mean ages of grades 1, 2, and 3 TS patients were all between 16.2 and 17.2 years. The ADD and ADD 2^0 TS groups were younger, averaging 9.2 and 10.1 years, respectively.

TABLE 1

SUMMARY OF CASES

GROUP AND DIAGNOSTIC CATEGORY	No. (%) Total	Males	Females	MALES/FEMALES
Present study:				
Controls	47 (14.5)	24 (51.1)	23 (48.9)	1.0
TS:				
Grade 1	43 (17.5)	34 (17.3)	9 (18.4)	3.8
Grade 2	145 (58.9)	118 (59.9)	27 (55.1)	4.4
Grade 3	58 (23.6)	45 (22.8)	13 (26.5)	3.5
All cases	246 (75.7)	197 (80.1)	49 (19.1)	4.0
ADD	17 (5.2)	13 (76.5)	4 (23.5)	3.3
ADD 2^0TS	15 (4.6)	14 (93.3)	1 (6.7)	14.0
All cases	325 100.0	249 76.3	77 23.7	3.2
Prior study:				
TS:				
Grade 1	31 (12.4)	28 (13.9)	3 (6.1)	9.3
Grade 2	147 (58.8)	116 (57.7)	31 (63.3)	3.7
Grade 3	72 (28.8)	57 (28.4)	15 (30.6)	3.8
All cases	250	201 (80.0)	49 (20.0)	4.1

TABLE 2

AGE OF INDIVIDUALS IN THE DIFFERENT DIAGNOSTIC CATEGORIES

DIAGNOSTIC CATEGORY (*N*)	AGE (Years) Mean ± SD	Mininum	Maximum
Controls:			
≤21 Years of age (34)	12.8 ± 3.3	6	19
>21 Years of age (14)	37.2 ± 6.0	27	53
All cases (47)	19.9 ± 12.0	6	53
TS:			
≤21 Years of age (191)	11.5 ± 3.9	2	21
>21 Years of age (55)	35.9 ± 11.9	22	70
All cases (246)	16.9 ± 12.1	2	70
Grade 1 (43)	16.2 ± 12.4	5	59
Grade 2 (145)	17.2 ± 12.4	4	70
Grade 3 (58)	16.8 ± 11.3	2	64
ADD (17)	9.2 ± 3.7	5	17
ADD 2^0 TS (15)	10.1 ± 9.0	5	36

TS in the Control Group

One of the advantages of a totally random control group is that if it is large enough it can give some indication of the frequency of tics and vocal noises in the general population. In our controls, one patient had both motor and vocal tics and one had vocal tics only (2.1% vocal tics, 4.2% motor tics). The one with both was a 15-year-old male with onset of ADD at age 2 years and had been treated with methylphenidate from age 2 to 7 years. He had been in EH classes throughout his schooling. He had problems with impatience and short temper and had been suspended from school twice for fighting. He touched things, including his crotch, excessively and occasionally exhibited himself. Motor and vocal tics had started at age 14 years.

The other individual with vocal tics was a 15-year-old male with mild ADD and a prior diagnosis of dyslexia. He had problems with sexual touching, head banging, and compulsive counting. Repeated throat clearing started at age 10 years and lasted 2 years. He satisfied the criteria for chronic motor-tic disorder, DSM III 307.22, which is a variation in the expression of the *TS* gene (Kidd et al. 1980; Baron et al. 1981; Pauls et al. 1981; Comings et al. 1984).

Prior Diagnoses

If ADD and emotional disturbance is an integral part of some TS patients, then the latter should show a higher frequency of having been previously diagnosed as minimally brain damaged (MBD), hyperactive, having ADD, or SED. The results of the question of whether a physician or professional had ever made any of these diagnoses prior to the patient's first visit to the Tourette Syndrome Clinic are shown in figure 1*A*. For the TS patients the most striking differences from controls were in the prior diagnoses of hyperactivity (χ^2 = 18.9; $P < .0005$) and ADD (χ^2 = 11.75; P = .0006). However, the prior

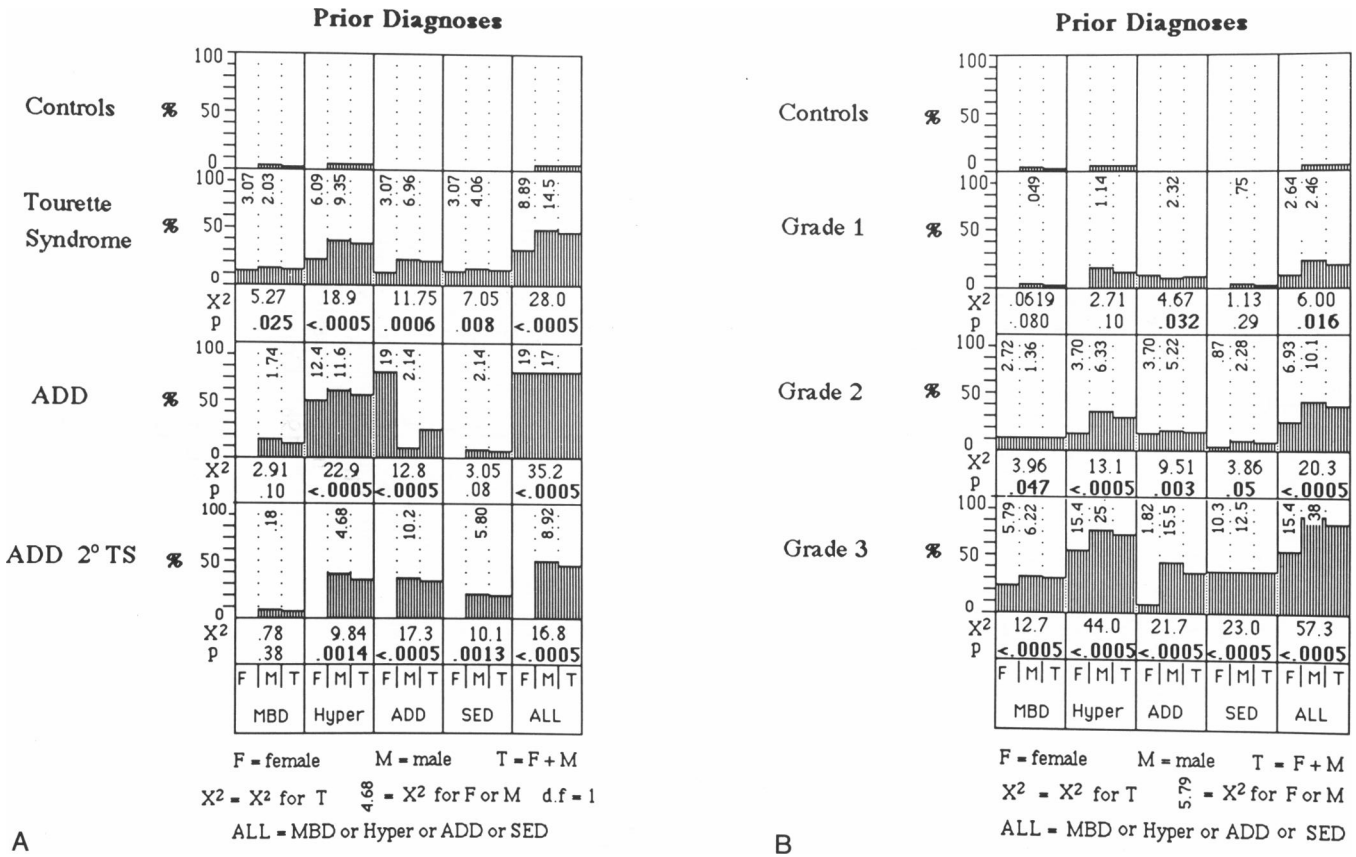


FIG. 1.—Frequency (in percent) of prior diagnoses of MBD, hyperactivity (Hyper), ADD, SED, or any of above (ALL) in (*A*) controls, TS, ADD, and ADD 2^0 TS groups and (*B*) controls and the three grades of TS. χ^2 and *P* values are given. The significant *P* values are boldface. Vertical values indicate the individual percentage figures.

diagnosis of SED was also common, with none so diagnosed in the control group and 15% so diagnosed in the TS group ($\chi^2 = 7.05$; $P = .008$). It was not surprising that the ADD patients had the highest frequency of prior diagnosis of hyperactivity and ADD. A prior diagnosis of SED was much less frequent in the ADD group, being but 7% ($\chi^2 = 3.05$; $P = .08$). The frequency of a prior diagnosis of SED was again significant in the ADD 2^0 TS group, being 20% ($\chi^2 = 10.1$; $P = .0013$). Since this group had negligible tics, this finding suggests that children with ADD 2° TS are more likely to be placed in SED classes than are those with "pure" ADD.

Comparison of prior diagnoses in the three grades of TS is shown in figure 1*B*. Even grade 1 patients showed a significant difference, both in prior diagnosis of ADD ($P = .032$) and in prior diagnosis of all categories combined ($P = .016$). Most striking were the grade 3 patients, in whom every category was significantly different from that in controls at $P < .0005$ and in whom 33% of both males and females had been previously diagnosed as SED.

These observations indicate that when prior independent diagnoses are used as an indicator, (1) TS patients show a significantly greater frequency of ADD and SED than do controls, (2) a prior diagnosis of SED is much more likely in TS and ADD 2^0 TS patients than in pure ADD patients, (3) even grade 1 TS patients had a prior diagnosis of ADD significantly more often than did controls, and (4) grade 3 TS patients have a very high frequency (33%) of prior diagnosis of SED. Although some of the SED diagnoses were made by professionals who were not familiar with TS and assumed that the tics were emotional in origin, in the majority of cases behaviors other than tics were responsible for this diagnosis.

Inattention

Each portion of the criteria for a diagnosis of ADD/ADDH has been examined to determine which is/are most different from that/those in controls. The five variables—FINISH, LISTEN, DISTR, CONC, and PLAY (see Methods)— are compared in figure 2*A*. In TS patients scores for all five were significantly different from those in controls at $P < .0005$. The three with the highest χ^2 values were CONC (68.8), DISTR (57.8) and LISTEN (50.3). For comparison, the results for the ADD and ADD 2^0 TS patients are also shown. Since all of these patients meet the criteria for ADD, they understandably show an even greater shift to the right. The results for the three grades of TS are shown in figure 2*B*. Remarkably, even in grade 1 cases (those who had tics too mild to treat), scores for the three categories of CONC, DISTR, and LISTEN were significantly different from those in controls at $P < .0005$. The profiles of the grade 3 cases closely resemble those of the ADD and ADD 2^0 TS patients.

Impulsivity

The five variables THINK, ORG, SUPER, CALL, and IMPAT (see Methods) were used to evaluate impulsivity and are shown in figure 3*A*. Again, in the TS patients scores for all variables were significantly different from those in controls at $P = < .0005$. The two with the highest χ^2 were SUPER (49.8) and

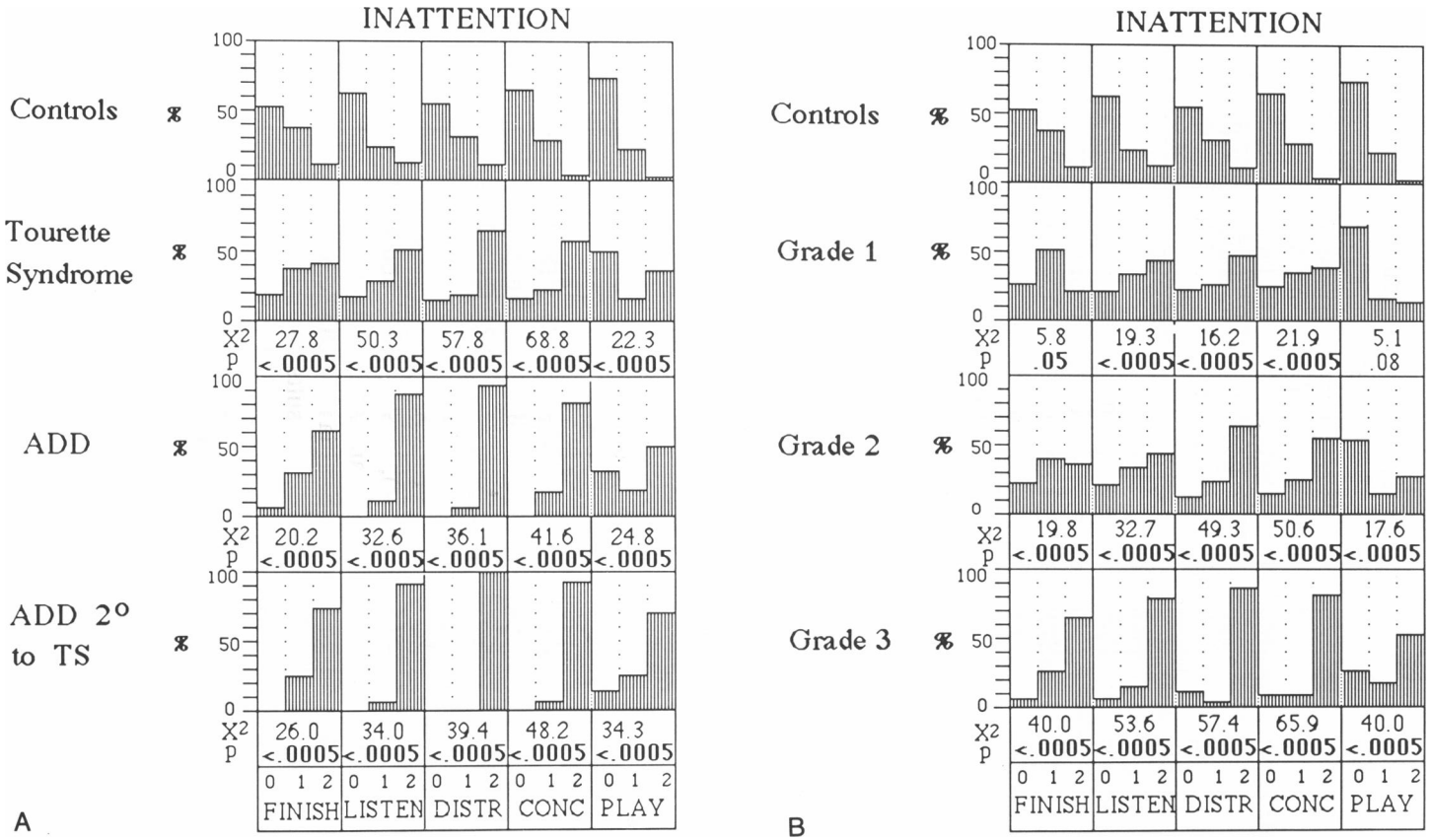


FIG. 2.—Frequency (in percent) of individual DSM III symptoms of inattention, where 0 = none, 1 = occasionally, and 2 = often. FINISH = fails to finish things started; LISTEN = seems not to listen to parents or teachers; DISTR = easily distracted; CONC = difficulty concentrating in school and elsewhere; and PLAY = difficulty sticking with play activities. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls and the three grades of TS. The χ^2 and *P* values are given. The significant *P* values are boldface.

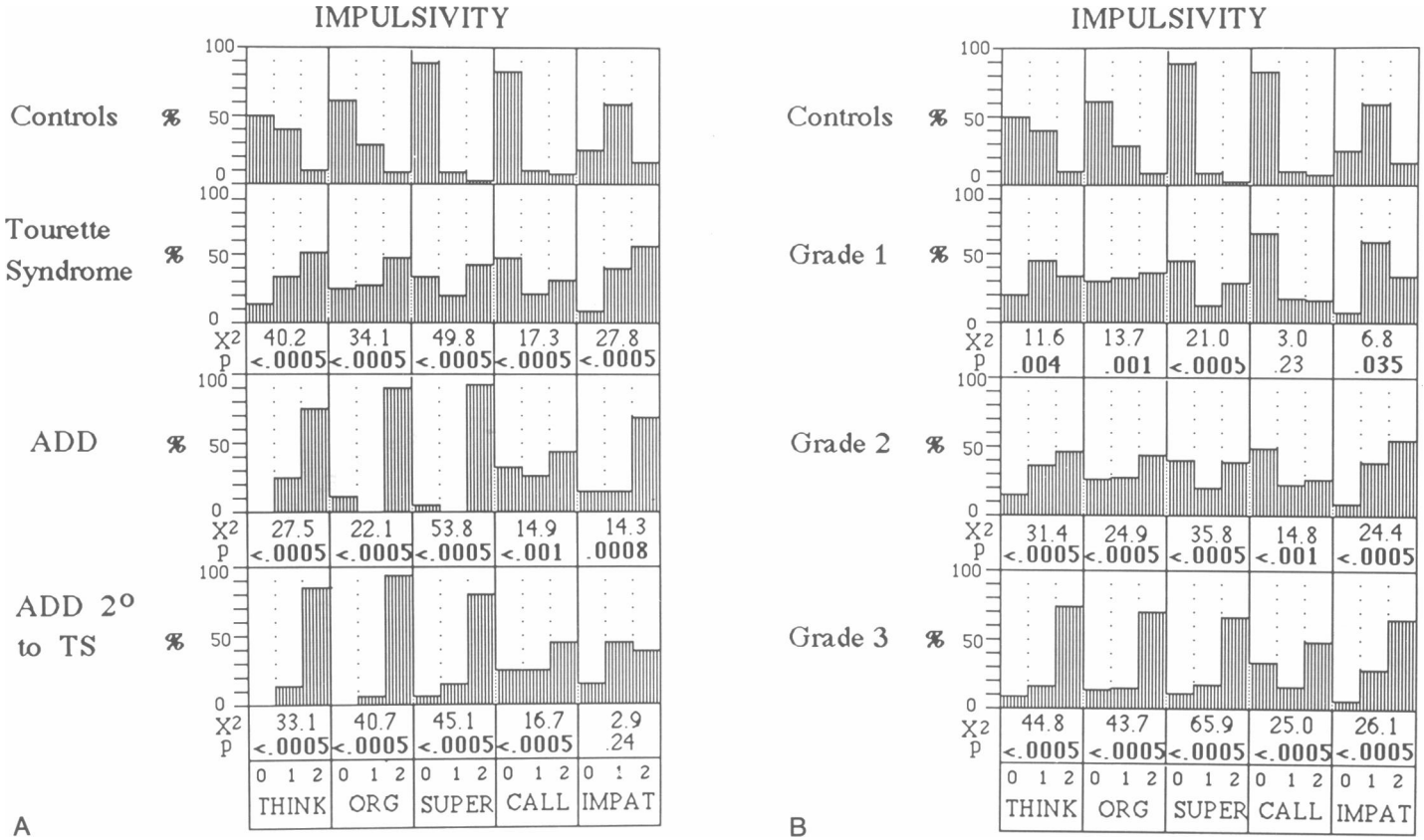


FIG. 3.—Frequency (in percent) of individual DSM III symptoms of impulsivity, where 0 = none, 1 = occasionally, and 2 = often. THINK = acts before thinking; ORG = trouble organizing work; SUPER = needs a lot of supervision; CALL = frequently calls out in class; and IMPAT = impatient. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls and the three grades of TS. The χ^2 and *P* values are given. The significant *P* values are boldface.

THINK (40.2). In grade 1 TS (fig. 3*B*), scores for THINK, ORG, SUPER, and IMPAT were all significantly different from those in controls at P .035–<.0005. In grade 2 TS scores for all variables were significantly different from those in controls at $P \leq .001$. The profiles for grade 3 TS again resembled those for ADD and ADD 2^0 TS.

ADD Score

The INATTENTION score represented the sum of the individual inattention variables, and the IMPULSIVITY score represented the sum of the individual impulsivity variables. The addition of these two gave the ADD score, with values ranging from 0 (for all negative) to 20 (for all positive). The distribution of these scores is shown in figure 4*A*. In the ADD and ADD 2^0 TS patients, all scores are ≥9. In the controls 6.3% of the subjects had scores ≥9. One of these individuals was the TS patient (score = 15) in the controls. In the TS patients 61.7% had scores ≥9. The distribution of the scores was significantly different from that in controls at a χ^2 of 74.7 and $P < .0005$. There was an even distribution of patients in all score ranges rather than the bimodal distribution that would be expected if there were two distinct TS groups (i.e., those with and without ADD). When the three grades of TS are examined separately (fig. 4*B*), grade 1 patients tend to be shifted to lower scores, grade 2 patients to be evenly distributed, and grade 3 patients to be shifted to the right. Despite this, even the grade 1 patients were significantly different from the controls at a χ^2 of 32.1 and $P < .0005$. By these criteria, 46.6% of grade 1, 57.9% of grade 2, and 82.8% of grade 3 TS patients had ADD.

Hyperactivity

The five variables RUN, SIT, SEAT, MOVE, and GO (see Methods) constitute the hyperactivity score (fig. 5*A*). Again, in TS patients scores for all five were significantly different from those in controls, at P .009–<.0005. Differences for SIT and SEAT were most significant, with χ^2 values of 50.7 and 44.5, respectively. MOVE and GO were least discriminatory. In grade 1 TS (fig. 5*B*), scores for SIT and SEAT were significantly different from those in controls at $P < .0005$, whereas the score for RUN was different at $P = .013$. In grades 2 and 3, scores for all variables were significantly different from those in controls at P .009–<.0005. The HYPERACTIVITY score, the sum of the individual variables, was significantly different from that in controls at a χ^2 of 39.8 and $P < .0005$. Not all ADD patients had hyperactivity, as indicated by the fact that 25% had a hyperactivity score of only 0–2. Grade 1 TS patients had scores significantly different from those of controls at $P = 0.002$, with an increasing shift to the right in grades 2 and 3.

ADDH Score

The ADDH score represented the sum of the ADD and HYPERACTIVITY scores. As with the ADD scores, the TS patients showed a uniform distribution in all levels of the score (fig. 6*A*). Individuals with ADDH had scores ≥18. The frequency of ADDH was 4.2% among controls, 48.8% among TS patients,

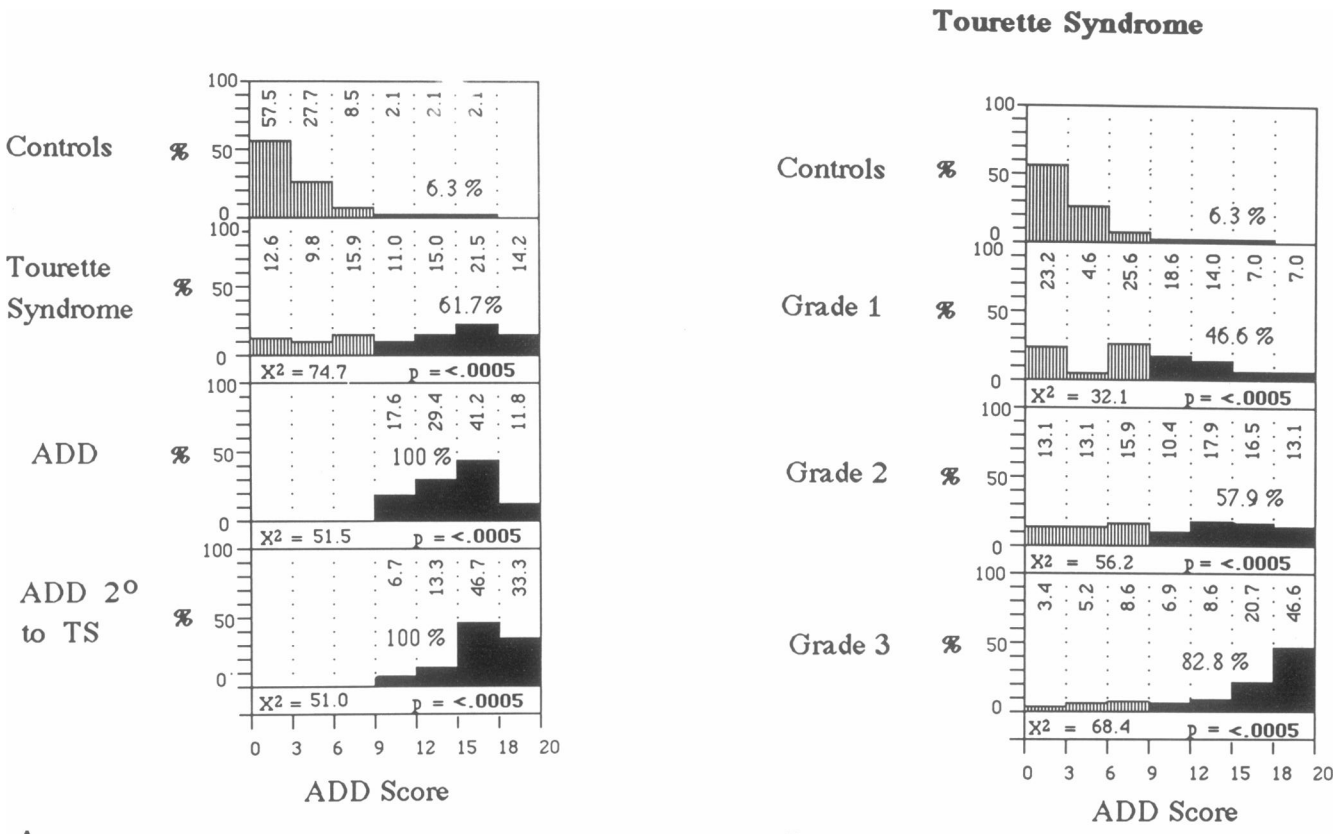


FIG. 4.—Frequency (in percent) of various ranges of the ADD score, which is a sum of the inattention and impulsivity scores. The ranges of, e.g., 3–6 are 3.1–6.0. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls and the three grades of TS. χ^2 and *P* values are given. The significant *P* values are boldface. Vertical values indicate the individual percentage figures.

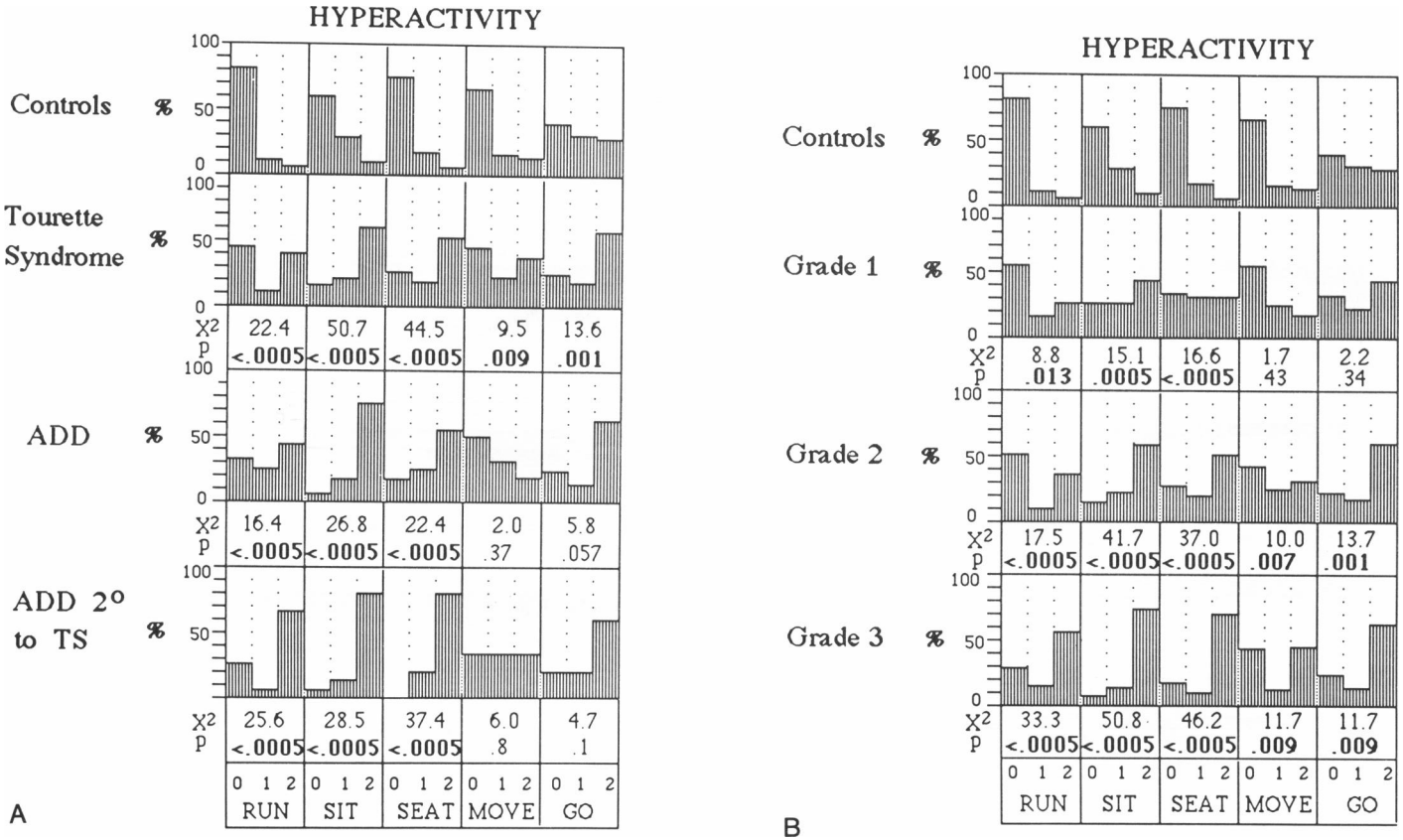


FIG. 5.—Frequency (in percent) of individual DSM III symptoms of hyperactivity, where 0 = none, 1 = occasionally, and 2 = often. RUN = runs about or climbs on things excessively; SIT = difficulty sitting still; SEAT = difficulty staying seated; MOVE = moves about excessively in sleep; and GO = always on the go. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls and the three grades of TS. The χ^2 and *P* values are given. The significant *P* values are boldface.

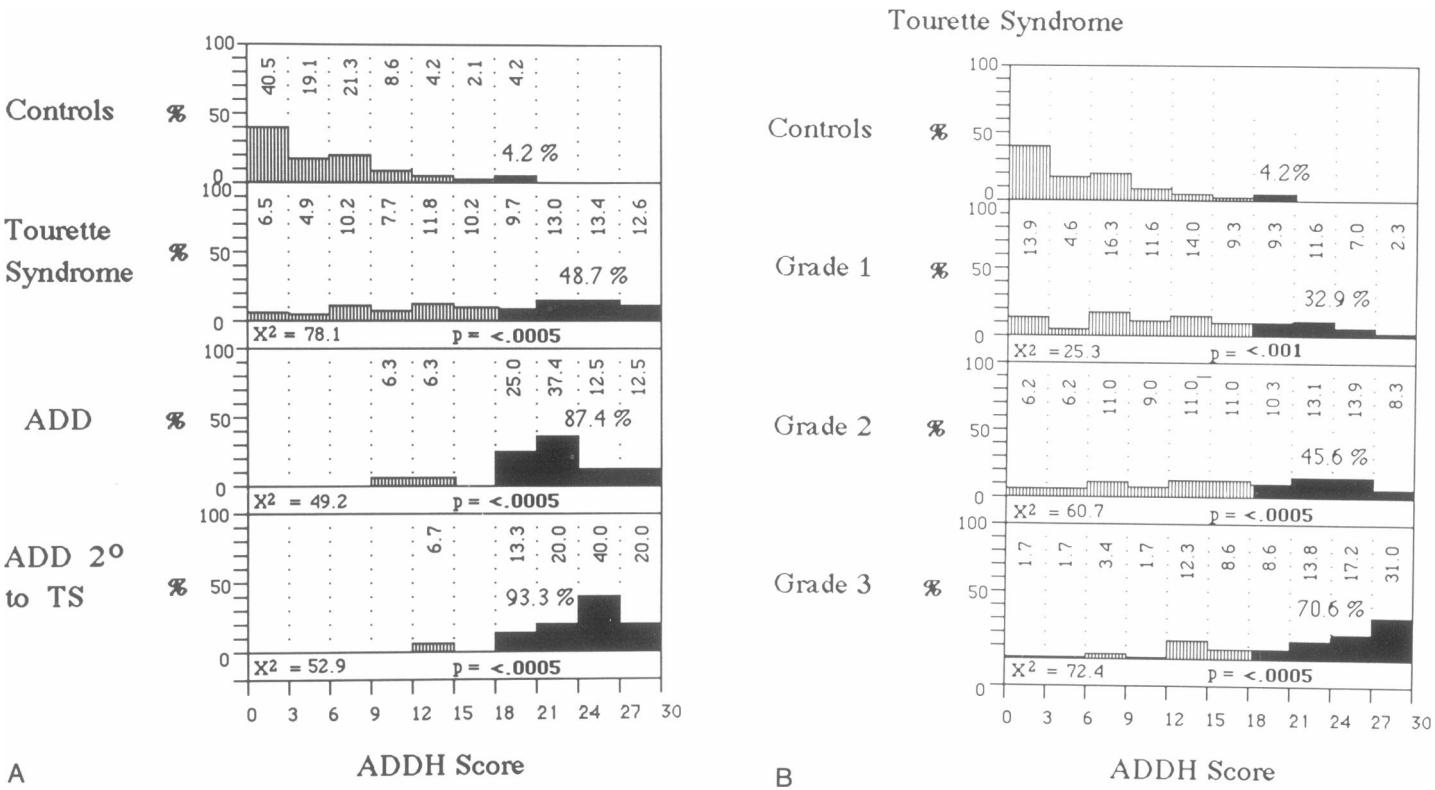


FIG. 6.—Frequency (in percent) of various ranges of the ADDH score, which is a sum of the ADD and hyperactivity scores. The ranges of, e.g., 3–6 are 3.1–6.0. *A*, Controls, TS, ADD, and ADD 2^0 TS groups; *B*, controls and the three grades of TS. χ^2 and *P* values are given. The significant *P* values are boldface. Vertical values indicate the individual percentage figures.

87.4% among ADD patients, and 93.3% among ADD 2^0 TS patients. The TS patient in the controls (ADDH score = 19) contributed one of the two highest values. The 48.7% frequency of ADDH in TS patients is similar to the 54% frequency in the first series (Comings and Comings 1984). Of patients age ≤21 years, 57% had ADDH scores ≥18 and 69% had ADD scores ≥9. Thus, there are significant attentional difficulties in more than two-thirds of all minors with TS.

Age at Onset of ADD and Tics

To determine the natural history of TS, it is necessary to obtain estimates of the age at onset of the major aspects of the disorder, viz., ADD and motor and vocal tics. These results are shown in table 3. The mean age at onset of ADD in those 159 cases who answered the appropriate questions was 4.28 years. There

TABLE 3

AGE AT ONSET OF ADD AND TICS IN TS

Diagnostic Category (*N*)	Mean ± SD
ADD:	
Males (130)	4.26 ± 2.88
Females (29)	4.38 ± 3.29
Grade 1 (23)	3.91 ± 2.68
Grade 2 (85)	4.40 ± 3.01
Grade 3 (51)	4.25 ± 3.00
All cases (159)	4.28 ± 2.95
Motor tics:	
Males (164)	7.07 ± 3.06
Females (42)	6.59 ± 2.94
Grade 1 (32)	7.43 ± 2.56
Grade 2 (124)	6.89 ± 3.05
Grade 3 (50)	6.88 ± 3.28
All cases (206)	6.97 ± 3.03
Vocal tics:	
Males (152)	7.80 ± 3.12
Females (35)	8.22 ± 3.11
Grade 1 (28)	7.67 ± 2.98
Grade 2 (118)	8.33 ± 3.03
Grade 3 (41)	6.75 ± 3.23
All cases (187)	7.88 ± 3.11
TS:	
Males (141)	6.72 ± 2.93
Females (34)	6.32 ± 3.13
Grade 1 (25)	7.36 ± 2.59
Grade 2 (112)	6.77 ± 2.94
Grade 3 (38)	5.81 ± 3.14
All cases (175)	6.65 ± 2.97
ADD–TS interval:	
Males (116)	2.50 ± 2.83
Females (24)	1.95 ± 3.00
Grade 1 (20)	2.15 ± 2.78
Grade 2 (77)	2.32 ± 2.78
Grade 3 (43)	2.67 ± 3.08
All cases (140)	2.41 ± 2.85

was no significant difference for males (4.26 years) versus females (4.38 years). In grade 1 cases with ADD, the age at onset was slightly lower (3.91 years) than those for grades 2 (4.40 years) and 3 (4.25 years).

The mean age at onset of motor tics was 6.97 years. It was similar for males (7.07 years) and females (6.59 years) and somewhat higher in grade 1 cases (7.43 years). The mean age at onset of vocal tics was 7.88 years, ~1 year later than that of the motor tics. In this case, the age at onset in females (8.22 years) was slightly later than that in males (7.80 years), and that in grade 3 cases was the lowest of all (6.75 years). The mean age at onset of TS was taken as the lesser of the ages at onset of motor or vocal tics, and data had to be available for both to be counted. This was 6.65 years. There was a gradient from grade 1 (7.36 years), to grade 2 (6.77 years), to grade 3 (5.81 years) cases.

There were two ways to estimate the mean duration between the age at onset of ADD and the age at onset of TS (motor or vocal tics). The first way was to simply subtract the mean age at onset of ADD (4.28 years) from the mean age at onset of TS (6.65 years), which gives 2.37 years. The second way was to determine this interval individually in all those cases for whom information was available on ADD and motor and vocal tics and then to take an average. Here the value was almost identical, 2.41 years (table 3). This result is similar to our previous estimate of 3.04 years (Comings and Comings 1984).

Use of Stimulant Drugs

Another way to determine the relationship between ADD and TS is to ask whether the use of stimulants or related drugs prior to being seen in the TS clinic was greater for TS patients than for controls. Table 4 shows the results. Only 2.1% of controls had previously been treated with methylphenidate, and this was the TS patient in the control group. By contrast, 26.8% of TS patients had previously been treated with Ritalin (methylphenidate). There were striking differences in the prior use of methylphenidate in the different grades of TS, increasing from 9.3% in grade 1, to 23.4% in grade 2, to 48.3% in grade 3.

TABLE 4

PRIOR DRUG USE (in %/Diagnostic Category)

	DIAGNOSTIC CATEGORY						
		TS					
DRUG	Controls	All Cases	Grade 1	Grade 2	Grade 3	ADD	ADD 2° TS
Ritalin	2.1	26.8	9.3	23.4	48.3	35.3	26.7
Cylert	0.0	10.2	7.0	6.2	22.4	17.6	6.7
Amphetamines	0.0	7.3	4.6	6.9	10.3	29.4	13.3
Imipramine	0.0	11.8	4.6	10.3	20.7	23.5	6.7
Mellaril	0.0	11.4	2.3	6.9	29.3	0.0	13.3
Any of above	2.1	39.0	18.6	34.5	65.5	70.6	33.0
χ^2 (any)	...	24.3	6.8	19.1	44.7	36.2	12.5
P	...	<.0005	.009	<.0005	<.0005	<.0005	<.0005

Comparable trends were seen for Cylert (pemoline), amphetamines, imipramine, and Mellaril (thioridazine). The frequency of the use of any of these medications was 2% for controls (the TS patient), 39% for all TS patients, 18.6% for grade 1, 34.5% for grade 2, 65.5% for grade 3, 75% for ADD, and 33% for ADD 2^0 TS. None of the ADD patients had previously been treated with Mellaril, whereas 33% of ADD 2^0 TS had received Mellaril. This disparity probably reflects the greater degree of behavior problems in the latter group (Comings and Comings 1987*a*).

Do Stimulants Cause TS?

Stimulants have been implicated as a cause or precipitating factor in TS (Golden 1974; Pollack et al. 1977; Bremness and Sverd 1979; Sleator 1980; Bachman 1981; Shapiro and Shapiro 1981; Lowe et al. 1982). An important question is whether TS patients who are treated with stimulants before the onset of tics (ADD→stimulants→tics) have an earlier age at onset of tics than do patients who received stimulants after their tics had already started (ADD→tics→stimulants). We investigated this previously (Comings and Comings 1984) and found that the time from ADD to tics was significantly greater in the ADD→stimulants→tics group, suggesting that stimulants were not precipitating the onset of tics. We were eager to reinvestigate this in the present study, in which questions were specifically designed to address this issue. The results of both studies are shown in table 5. Again the ADD→stimulants→tics group showed a greater ADD-to-tic interval (3.69 years) than did the ADD→tics→stimulants group (2.24 years). When those individuals in whom the ADD-to-tics interval was <1 year were removed (see previous study

TABLE 5

TIME FROM ONSET OF ADD TO ONSET OF TICS (ADD–TS)

Group and Sequence (*N*)	Mean ± SD ADD–TS (Years)	*t*-Test	*P*
Present study:			
All TS patients (140)	2.41 ± 2.85		
Treated with stimulants:			
ADD→stimulants→tics (23)	3.69 ± 2.56	2.07	<.05
ADD→tics→stimulants (41)	2.24 ± 2.76		
Correction for ADD-tics ≤ 1 year:			
ADD→stimulants→tics (20)	4.25 ± 2.27	0.90	NS
ADD→tics→stimulants (27)	3.63 ± 2.38		
Prior study:			
All TS patients (91)	3.04 ± 2.94		
Treated with stimulants:			
ADD→stimulants→tics (18)	5.31 ± 2.70	5.19	<.001
ADD→tics→stimulants (35)	1.61 ± 2.33		
Correction for ADD-tics ≤ 1 year:			
ADD→stimulants→tics (18)	5.31 ± 2.70	1.68	NS
ADD→tics→stimulants (20)	4.00 ± 2.10		

NOTE.—NS = not significant.

[Comings and Comings 1984] for rationale), the results were in the same direction, with the ADD→stimulants→tics group showing a mean of 4.25 years from ADD to tics and the ADD→tics→stimulants group showing an ADD-to-tic interval of 3.63 years. In the prior study the results were 5.31 and 4.00 years, respectively. This validates the previous conclusion that, on average, the administration of stimulants to children with ADD does not hasten the onset of tics. This greater ADD-to-tic interval in the ADD→stimulants→tics group is not due to finally producing a drug-induced TS in children who would not otherwise develop TS, since the frequency of a positive family history of TS (~75%) was the same in both groups (Comings and Comings 1984).

How Do Stimulants Affect the Tics?

There were a total of 92 patients who indicated that they were on stimulants during the time that they had tics. Table 6 shows the results of the question as to the effect that stimulants had on the tics. Of the ADD→tics→stimulants patients, 25% gave no answer, 23% said that there was no effect, 13% said that the tics were better, 15% said that the tics were slightly worse, and 23% said that the tics were much worse. Of the ADD→stimulants→tics patients, 72% gave no answer, 9% said that there was no effect, 3% said that the tics were slightly worse, and 3% said that the tics were much worse. These differences are understandable in that those patients who had tics before being placed on stimulants would be better able to judge whether the tics were worse than would those who developed tics while being on stimulants. In sum, the patients were approximately equally divided between no effect or better (31.5%) and slightly or much worse (27.2%). The vast majority of these patients were not on haloperidol. Administration of haloperidol usually alleviated the tics in those who were otherwise benefiting from the stimulant medication.

There were 28 patients who stated that they were actually on stimulants when the tics first started. Of these, 17 were able to give an estimate of the duration of time between the start of stimulants and the onset of tics. The mean duration was 6.4 mo, with a range of 2 days–2 years. The mean ± SD ADD-to-tics interval in the 10 of these 17 for whom information was available was 3.50 ± 1.90 years. Since the average interval from ADD to tics for all TS patients was 2.4 years, this result suggests that in this group the onset of tics was more or less due and that in most of them the ADD-to-tic interval had not been

TABLE 6

EFFECT OF STIMULANTS ON TICS

SEQUENCE (*N*)	NO. (%) OF CASES				
	No Answer	No Effect	Better	Slightly Worse	Much Worse
ADD→tics→stimulants (60)	15 (25.0)	14 (23.3)	8 (13.4)	9 (15.0)	14 (23.3)
ADD→stimulants→tics (32)	23 (71.9)	3 (9.4)	4 (12.5)	1 (3.1)	1 (3.1)
Total (92)	38 (41.3)	17 (18.5)	12 (13.0)	10 (10.9)	15 (16.3)

shortened by treatment with stimulants. Price et al. (1986) have examined the question of the effect of stimulants on the precipitation of TS symptoms by studying identical twins, one of which was treated with stimulants while the other was not. All of the untreated cotwins developed TS, and there was no significant difference in the age at onset of the symptoms. Of 34 TS patients treated with stimulants, they found that 24% showed treatment-associated exacerbation of the tics. This result is very similar to our finding that 27% of stimulant-treated patients showed a moderate or significant increase in tics.

Effect of Stimulants on ADD

Is ADDH associated with TS less responsive to stimulant medication than is pure ADD? To evaluate this, the parents were asked about the effect of stimulants on (1) hyperactivity, (2) concentration, and (3) school performance (table 7). The medication was more effective in the pure ADD children (90%, 80%, and 78% were somewhat or much better in these three areas, respectively) than in TS patients (50%, 54%, and 52% were somewhat or much better). However,

TABLE 7

THERAPEUTIC EFFECT OF STIMULANT TREATMENT

DIAGNOSIS (*N*)	No. (%) of Cases			
	No Effect	Somewhat Better	Much Better	Worse
Effect on hyperactivity:				
Controls (1)	0	1 (100)	0	0
TS:				
Grade 1 (9)	5 (55.5)	1 (11.1)	0 (0.00)	3 (33.3)
Grade 2 (43)	10 (23.3)	9 (20.1)	14 (32.5)	10 (23.2)
Grade 3 (30)	2 (6.70)	10 (33.3)	8 (26.7)	10 (33.3)
Total (82)[a]	17 (20.7)	20 (23.4)	22 (26.8)	23 (28.0)
ADD (10)	1 (10.0)	1 (10.0)	7 (80.0)	1 (10.0)
ADD 2^0 TS (4)[b]	0 (0.00)	1 (25.0)	2 (50.0)	1 (25.0)
Effect on concentration:				
Controls (1)	0	1 (100)	0	0
TS:				
Grade 1 (9)	5 (55.6)	2 (22.2)	1 (11.1)	1 (11.1)
Grade 2 (42)	9 (21.4)	9 (21.4)	16 (38.1)	8 (19.0)
Grade 3 (32)	6 (18.7)	8 (25.0)	9 (28.1)	9 (28.1)
Total (83)[a]	20 (24.1)	19 (22.9)	26 (31.3)	18 (21.7)
ADD (9)	0 (0.00)	1 (11.1)	7 (77.8)	1 (11.1)
ADD 2^0 TS (4)[b]	0 (0.00)	1 (25.0)	2 (50.0)	1 (25.0)
Effect on school performance:				
Control (1)	0	1 (100)	0	0
TS:				
Grade 1 (8)	5 (62.5)	2 (25.0)	1 (12.5)	0 (0.00)
Grade 2 (41)	12 (29.3)	8 (19.5)	12 (29.3)	9 (22.0)
Grade 3 (26)	4 (15.3)	7 (26.9)	9 (34.6)	6 (38.4)
Total (75)[a]	21 (28.0)	17 (22.7)	22 (29.3)	15 (20.0)
ADD (9)	0 (0.00)	1 (11.1)	6 (66.7)	2 (22.2)
ADD 2^0 TS (4)	0 (0.00)	1 (25.0)	2 (50.0)	1 (25.0)

[a] Differs from ADD at $P < .0005$ (by χ^2).
[b] Differs from ADD at $P < .025$ (by χ^2).

in the ADD 2^0 TS patients, in whom the evaluation was not complicated by the presence of many tics, 75% were somewhat or much better in all three categories (although the numbers are very small). In many TS patients with significant ADD, the combined use of haloperidol and methylphenidate is more effective than either drug is alone.

ADD 2^0 TS

Although there have been several reports suggesting a strong genetic influence in ADD (Morrison and Stewart 1971, 1974; Shafer 1973; Cadoret et al. 1975; Cantwell 1976; Welner et al. 1977), the concept of a subcategory, ADD with or without hyperactivity (ADD/H) secondary to a *TS* gene, is new (Comings and Comings 1984). The criteria for this diagnosis are as follows:

1. Satisfy the DSM III criteria of ADDH.
2. Have occasional mild motor or vocal tics but not both and/or have a family history of TS or motor tics or vocal tics.

Of the 15 cases in this category, three had a family history of TS, nine had mild motor or vocal tics, and three had both a positive family history and mild motor or vocal tics. Our clinical impression is that, as a group, these individuals have more problems with behavior and conduct than do pure ADDH patients. This is discussed and quantitated in Part II (Comings and Comings 1987*a*).

Constituting the rationale for this diagnostic category are the following:

1. The majority of TS patients also have ADD or ADDH (see above).
2. In the majority of TS patients the natural history of the disease was to first present as ADDH and then, after an average of 2.4 years, to develop motor and vocal tics.
3. Siblings of children with TS were often found to have ADDH. We have observed the subsequent development of tics and vocal noises in 10 of these children.
4. Genetic studies (see above) indicate that ~1.2% of the population carries a *TS* gene and that 70%–100% of male carriers will manifest the gene in some manner (Comings et al. 1984; Devor 1984; Pauls and Leckman 1986). If 69% of these males (< age 21 years) have ADD (see above), then $1.2 \times .9 \times .69$ or ~0.75% of males will at some time in their life have ADD due to a *TS* gene. Depending on the frequency of ADD in male children (2.5%–8%), this suggests 10%–30% of ADD in male children will be due to a *TS* gene. A comparable percentage holds for females.

Segregation of TS and ADD

In the above discussion we have assumed that the *TS* gene is one of the causes of ADD and that ADD is one of the pleiotrophic effects of the *TS* gene. This assumption is strengthened by the observation that intracerebral injection of dopamine (Jackson et al. 1975) and some neuropeptides, such as bombesin, result in both motor hyperactivity and stereotyped behaviors in rats (Pert et al. 1980; Merali et al. 1983; Schultz et al. 1984). As discussed in the final paper in this series (Comings 1987), TS is best visualized as an imbalance of mesocortical and mesolimbic dopamine neurons resulting in ADD and TS. However,

TABLE 8

COSEGREGATION OF TS WITH ADD

SAMPLE	*N* (% WITH ADD/H)		
	Proband Status		
	With ADD/H	Without ADD/H	Total
Probands	19 (100)	5 (0)	24 (79)
Nonprobands with TS or CMT, or obligate carriers[a]	91 (37)	19 (21)	110 (34[c])
Unaffected non-TS[b]	57 (3.5)	8 (12.5)	65 (4.6[c])
Total	167	32	199

NOTE.—CMT = chronic motor or vocal tics but not both.

[a] Obligate carriers have a child and a sibling or parent with TS.

[b] The preponderance of affected over unaffected in these families is due to the fact that they were selected from a total of 700 families having a high number of affecteds, thus being ideal for linkage studies.

[c] $P < .0005$ (by $\chi^2 = 20.87$) for nonprobands with TS or CMT, or obligate carriers, vs. unaffected non-TS.

Pauls et al. (1986) have recently suggested that the two disorders may segregate independently. This suggestion was based on a small number of families in which the risk of ADDH in relatives of TS patients with ADDH was 22.4% whereas the risk for ADDH in relatives of individuals with TS without ADDH was 2.8%. This disparity did not appear to be due to two separate *TS* genes, one with and the other without ADD, since in the TS-and-ADD families the two traits seemed to segregate independently. Seventy percent of their TS probands had TS and ADD. This is unlikely to be simply due to severe ascertainment bias, whereby only individuals with both TS and ADD seek medical care, since (1), as shown in figure 4*B*, even among grade 1 TS patients 47% had ADD and (2) the symptoms of ADD are such an integral part of TS.

To investigate this aspect of the problem, we have examined the segregation of TS and ADD and of motor or vocal tics and ADD/H in 25 families used in linkage studies (Comings et al. 1986*a*, 1986*b*). In families in which the proband had ADD/H, 37% of the nonproband TS patients had ADD/H and 3.5% of the non-TS patients had ADD/H (table 8). In families in which the proband did not have ADD/H, 21% of the nonproband TS patients had ADD/H and 12.5% of the non-TS patients had ADD/H. There was no significant difference in the frequency of ADD/H in nonproband TS patients whether the proband had ADD/H or not, and there was no significant difference in the frequency of ADD/H in non-TS patients whether the proband had ADD/H or not. In contrast, there was a highly significant difference ($P < .0005$) in the frequency of ADD/H in all nonproband TS patients (34%) versus all non-TS patients (4.6%). These results do not support those of Pauls et al. (1986) and indicate that TS and ADD do segregate together. The critical difference is that, when a large number of patients are studied, it is apparent that although assertainment bias does increase the frequency of ADD/H in TS, it increases it from ~30% in mild cases to 70% in severe cases, not from 0% in mild to 70% in severe cases. This is discussed in more detail elsewhere (Comings and Comings, in press).

Special Classes

Determination of the frequency with which a patient had attended special classes provided an unbiased and practical estimate of learning problems. In California, placement in special classes requires extensive evaluation by school psychologists. The general rule is that a child must be ≥2 years behind his peers to qualify for EH, LD, or LH classes. Children who have very severe behavioral problems are placed in SED classes. Table 9 shows the frequency of placement in special classes for the different diagnostic groups. The TS patient in the controls accounted for the 2.1% of control patients placed in EH classes. For all TS patients, 13% attended EH and LH classes; and 31% of grade 3 TS patients attended EH classes ($P < .0005$). The presence of ADD was the primary factor, since 19.7% of TS patients with ADD attended EH classes whereas only 2.1% without ADD attended such classes.

The results with attendance in SED classes were most striking. Here, 17% of all TS patients were placed in SED classes, compared with 2.1% of controls. All three grades of TS showed significant differences from controls. Being placed in an SED class may be partially biased by the fact that many psychologists evaluating these children still believe that motor tics are a sign of serious emotional disturbance and thus conclude that such children belong in SED classes. However, as shown in Part II (Comings and Comings 1987*a*), conduct problems are common in TS. The fact that behavior and conduct themselves account for a significant part of the placement in SED classes is demonstrated by the finding that significantly more children with grade 1 TS (18.6%) were placed in SED classes than were controls (0%) ($P = .009$), despite that fact that in grade 1 the tics are too mild to justify treatment. This is consistent with our clinical observations that a *TS* gene can result in severe behavioral problems despite very mild motor or vocal tics. This is also consistent with our pedigree studies indicating that significant behavioral problems are often seen in first-degree relatives of TS patients with no motor or vocal tics. Proving that they do in fact carry a *TS* gene must await the development of a marker for the *TS* gene. When all types of special classes are combined, all diagnostic categories are significantly different from the controls ($P < .0005$) in that 35% of all TS patients, compared with only 6.3% of controls, were placed in some type of special class.

Other School Problems

To obtain another estimate of school problems, the parents and patients were asked whether the latter ever had required a special teacher or a home teacher and whether they had flunked or been advanced a grade. Of all TS patients 33.7% had required a special teacher, compared with only 8.5% of controls ($P < .0005$; table 10). In grade 1 TS, 18.6% had required a special teacher ($P = .16$); in grade 2, 29.1% ($P = .002$), and in grade 3, 55.2% ($P < .0005$). This was partly related to whether the TS patient had ADD, since among those with ADD 42.7% required a special teacher ($P < .0005$), whereas among those without ADD 19.2% required a special teacher ($P = .05$). Fifty percent of the ADD patients and 47% of the ADD 2^0 TS patients required a special teacher.

TABLE 9

FREQUENCY OF PLACEMENT IN SPECIAL CLASSES

SPECIAL CLASS	DIAGNOSTIC CATEGORY								
		TS							
	Controls	All Cases	Grade 1	Grade 2	Grade 3	+ ADD	− ADD	ADD	ADD 2[0] TS
EH:									
%	2.1	13.0	4.7	8.3	31.0	19.7	2.1	25.0	20.0
χ^{2a}	...	6.86	2.26	4.16	17.5	10.9	1.00	11.8	9.88
P	...	**.009**	.14	**.04**	**<.0005**	**.001**	.16	**.0006**	**.001**
LH:									
%	2.1	13.0	9.3	10.3	22.4	23.7	3.2	37.5	26.7
χ^2	...	4.70	2.22	3.14	9.27	11.1	.14	14.1	9.29
P	...	**.03**	.14	.08	**.0016**	**.001**	.71	**<.0005**	**.0016**
SED:									
%	2.1	17.0	18.6	14.5	22.4	19.7	12.8	18.8	6.8
χ^2	...	7.02	6.80	5.37	9.27	8.47	4.28	5.14	.80
P	...	**.008**	**.009**	**.02**	**.0016**	**.002**	**.04**	**.02**	.37
Any of above:									
%	6.4	35.0	23.6	28.3	60.3	46.0	17.6	62.5	46.7
χ^{2a}	...	17.7	7.20	11.8	35.7	27.0	4.85	24.4	16.5
P	...	**<.0005**	**.008**	**.0006**	**<.0005**	**<.0005**	**.03**	**<.0005**	**<.0005**

NOTE.—Significant *P* values are boldface.

[a] For this category, the contribution of the TS patient in the controls was excluded for the χ^2 tests.

TABLE 10

FREQUENCY OF VARIOUS SCHOOL PROBLEMS

SCHOOL PROBLEM	DIAGNOSTIC CATEGORY								
		TS							
	Controls	All Cases	Grade 1	Grade 2	Grade 3	+ ADD	− ADD	ADD	ADD 2° TS
Special teacher required:									
%	8.5	33.7	18.6	29.7	55.2	42.7	19.2	50.0	46.7
χ^{2a}	...	14.2	3.11	10.6	27.8	21.0	4.04	16.1	13.6
P	...	**<.0005**	**.08**	**.001**	**<.0005**	**<.0005**	**.05**	**<.0005**	**.0007**
Home teacher required:									
%	0.0	13.0	4.6	11.0	24.1	17.1	5.3	25.0	13.3
χ^2	...	6.86	2.21	5.64	13.1	9.24	2.58	11.7	6.45
P	...	**.009**	.14	**.02**	**<.0005**	**.0016**	.11	**<.0005**	**.01**
Held back one grade:									
%	8.5	26.4	23.3	22.7	37.9	32.9	16.0	31.3	20.0
χ^2	...	5.67	2.74	3.46	10.5	10.8	1.51	3.98	.95
P	...	**.02**	.10	.07	**.001**	**.001**	.22	**.05**	.33
Skipped one grade:									
%	4.2	4.88	7.0	4.8	3.5	2.0	9.6	0.0	0.0
χ^2	...	.040	.34	.029	.035	.71	1.27	.73	.65
P	...	.77	.56	.76	.77	.17	.26	.39	.42
Test anxiety:									
% None	46.8	39.0	37.2	40.0	37.9	44.6	28.7	52.9	66.7
% Mild	34.0	30.9	39.5	31.0	24.1	23.0	43.6	29.4	20.0
% Moderate	19.2	13.0	16.5	7.0	13.8	13.1	12.8	11.8	13.3
% Severe	0.0	17.1	16.3	15.2	22.4	19.1	14.9	5.9	0.0
χ^2 (Severe)	...	9.4	8.3	8.1	12.0	10.5	7.8	2.8	...
P	...	**.0015**	**.002**	**.002**	**.0005**	**.001**	**.005**	**.09**	...
Stuttering:									
%	6.4	31.3	34.8	24.8	44.8	36.8	22.3	18.6	33.3
χ^2	...	12.3	11.5	7.4	19.2	15.9	5.61	1.8	7.3
P	...	**<.0005**	**.0008**	**.007**	**<.0005**	**<.0005**	**.02**	.18	**.007**

NOTE.—Significant *P* values are boldface.

[a] For this category, the contribution of the TS patient in the controls was excluded for the χ^2 tests.

The requirement of a home teacher sometime during patient schooling is a special—but more severe—case. Such a requirement usually indicated that there were such severe problems in school that some home teaching was deemed necessary. The message usually is, "We cannot tolerate your child in our classroom, so we will send the teacher to you." That this is an indication of severe problems is indicated by the fact that none of the controls required a home teacher, compared with 13% of all TS patients. This was even more related to the presence of ADD, since 17.1% of such patients required a home teacher ($P = .0016$) compared with only 5.3% of TS patients without ADD ($P = .11$).

Among the controls 8.5% had been held back a grade, compared with 26.4% of all TS patients. ($P = .02$). For grade 1 TS patients, 23% had been held back a grade, compared with 37% for grade 3.

Interestingly, there were no significant differences between controls and any of the diagnostic categories in the frequency of being advanced a grade. This occurred in 4.2% of controls, 4.9% of all TS patients, and 7.0% of grade 1 TS patients. This is a reflection of the heterogeneity of the TS phenotype. TS patients have a normal and sometimes outstanding IQ, and thus it is not surprising that, if specific learning problems or the presence of ADDH do not hold them back, they can do quite well. Even 3.5% of the grade 3 TS patients had been advanced a grade. These extremes highlight some of the conceptual problems with a diagnosis of TS. Although some can have significant school and behavioral problems, many do not—and we must guard against thinking that just because some have problems they all will. Each must be treated as an individual, the same as children without TS. None of the ADD or ADD 2^0 TS had been advanced a grade.

Test Anxiety

Severe test anxiety was present in 17.1% of all TS patients and in none of the controls ($P = .0015$). Its occurrence was significantly greater in all three grades of TS. That this is an integral aspect of TS and not simply due to ADD is indicated by the fact that severe test anxiety was not significantly greater for ADD patients (5.9%) than for controls and that significant differences from controls were noted for both TS patients with ADD (19.1%; $P = .001$) and TS patients without ADD (14.9%; $P = .005$).

Stuttering

Many TS patients have various types of speech problems, including talking so rapidly that they are difficult to understand. When queried about ever having had problems with stuttering, only 6.25% of controls reporting having had problems, whereas 31.3% of all TS patients reported having had such problems ($P = <.0005$). All three grades of TS were significantly different from controls. The high incidence of stuttering in grade 1 TS patients (34.8%) suggests that stuttering is not simply due to motor or vocal tics. By contrast, the increased frequency of stuttering in ADD patients (18.6%) was not significantly different from that in controls, whereas 33.3% of children with ADD 2^0 TS stuttered.

This and the fact that stuttering was significant for both TS patients with ADD and TS patients without ADD suggests that stuttering is a primary result of the presence of the *TS* gene.

Reading Problems

To assess reading problems, six different questions were asked (see Methods). The results are shown in table 11. With the exception of letter reversal in grade 1 TS, significant differences from controls were seen in all diagnostic categories for letter, number, and word reversal. Dropping of words occurred so often in controls (16.6%) that the frequency was not significantly different from that for any category. Problems with reading slowly were seen in 10.4% of controls and in 28.1% of all TS patients ($P = .01$). The most significant differences occurred with respect to retention. Among controls 8.3% had problems with poor retention, whereas 41.5% of all TS patients had such problems ($P < .0005$). Even among grade 1 TS patients, 27.9% had problems with poor retention ($P = .016$). This finding confirms our clinical impression that one of the most frequent complaints of parents, teachers, and patients is that some TS children cannot retain or remember what they have read. Parents make remarks such as, "His mind is like Teflon™, nothing sticks." In addition to interfering with the learning of academic subjects, poor retention also interferes with the learning of social skills, a circumstance that produces its own set of problems. The difficulties with retention can sometimes be improved with methylphenidate.

Reading-Problem Score

To examine all six variables simultaneously, a positive result on any one of them was counted as one, giving a reading-problem score with a maximum value of 6. The distributions for this score are shown in figure 7. All TS patients were significantly different from controls at $P < .005$. The mean ± SD score for controls was 0.56 ± 0.96. Only grade 1 TS patients, with a mean ± SD score of 1.28 ± 1.64, were not significantly different from controls. The presence of ADD clearly played a significant role, since the distribution of reading scores in TS patients without ADD was not significantly different from that in controls (fig. 7*C*), whereas the distribution in those with ADD was very significantly different ($P < .0005$). The correlation coefficient between the ADD score and the reading score was .44, and that between the ADDH score and the reading score was .41. The linear regression equation was as follows: ADD score = 8.4 + 1.58 (reading score); and ADDH score = 13.1 + 2.03 (reading score).

School Performance

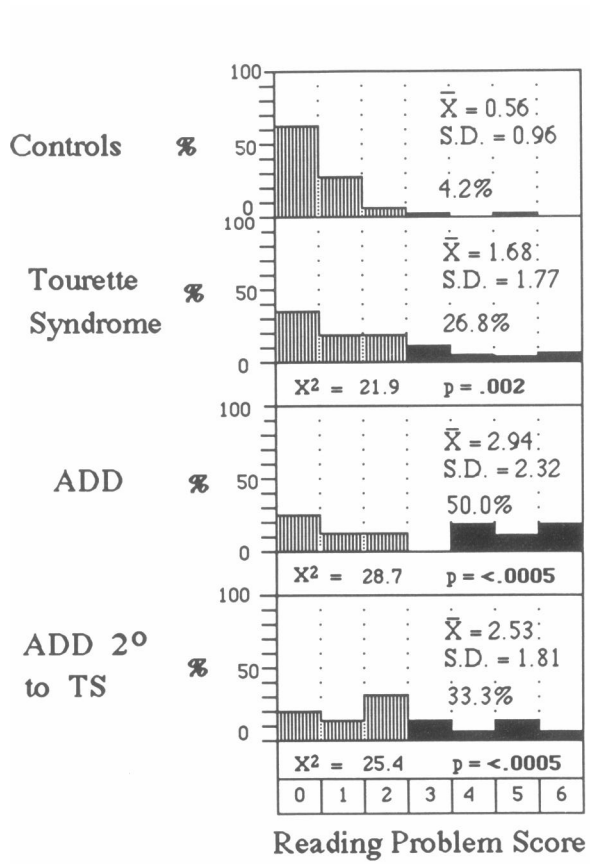
The results of assessment of school performance (see Methods) are shown in figure 8. The TS patients were significantly different from the controls in the three categories of math, reading, and writing, both in grade school and in high school. The χ^2 values were highest for math, next highest for writing, and lowest for reading. For the grade-school years, the ADD patients had even higher χ^2 values. The values for ADD patients in high school were similar to

TABLE 11

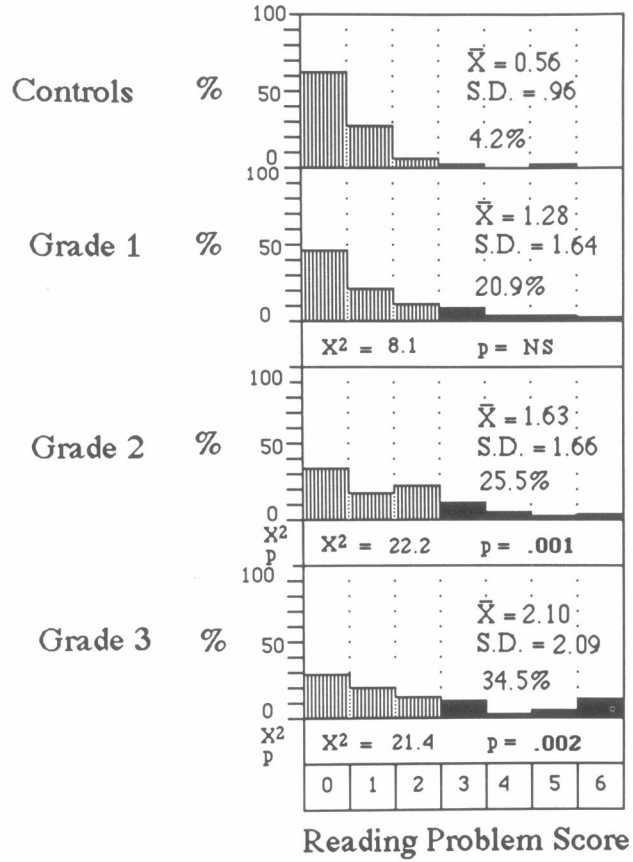
READING PROBLEMS

READING PROBLEM	DIAGNOSTIC CATEGORY						
		TS					
	Controls	All Cases	Grade 1	Grade 2	Grade 3	ADD	ADD 2^0 TS
Letter reversal:							
%	14.9	32.5	27.9	32.4	36.2	58.8	53.3
χ^2	...	7.39	3.20	6.82	7.44	14.1	10.7
P	...	**.007**	**.08**	**.01**	**.007**	**<.0005**	**.001**
Number reversal:							
%	2.1	19.5	14.0	19.3	24.1	47.0	46.7
χ^2	...	11.0	7.05	10.6	13.1	25.22	24.7
P	...	**.001**	**.008**	**.001**	**<.0005**	**<.0005**	**<.0005**
Word reversal:							
%	4.2	19.1	16.3	17.9	24.1	41.2	20.0
χ^2	...	6.29	3.66	5.35	8.0	14.2	3.85
P	...	**.01**	**.05**	**.02**	**.002**	**<.0005**	**.05**
Drops words:							
%	16.6	27.6	23.3	27.6	31.0	35.3	40.0
χ^2	...	2.49	.63	2.29	2.91	2.58	3.59
P	...	.12	.43	.14	.09	.11	.06
Reads slowly:							
%	10.4	28.1	18.6	26.2	39.7	43.7	40.0
χ^2	...	6.55	1.23	5.11	11.4	7.83	6.88
P	...	**.01**	.27	**.02**	**.0007**	**.005**	**.009**
Poor retention:							
%	8.3	41.5	27.9	40.0	55.2	52.9	53.3
χ^2	...	18.8	5.93	16.3	25.4	15.4	14.9
P	...	**<.0005**	**.016**	**<.0005**	**<.0005**	**<.0005**	**<.0005**

NOTE.—Significant *P* values are boldface.


Controls
%
100
50
0
X̄ = 0.56
S.D. = 0.96
4.2%
Tourette
Syndrome
%
X̄ = 1.68
S.D. = 1.77
26.8%
X² = 21.9
p = .002
ADD
%
X̄ = 2.94
S.D. = 2.32
50.0%
X² = 28.7
p = <.0005
ADD 2°
to TS
%
X̄ = 2.53
S.D. = 1.81
33.3%
X² = 25.4
p = <.0005
0 1 2 3 4 5 6
Reading Problem Score

A


Controls
%
100
50
0
X̄ = 0.56
S.D. = .96
4.2%
Grade 1
%
X̄ = 1.28
S.D. = 1.64
20.9%
X² = 8.1
p = NS
Grade 2
%
X̄ = 1.63
S.D. = 1.66
25.5%
X²
p
X² = 22.2
p = .001
Grade 3
%
X̄ = 2.10
S.D. = 2.09
34.5%
X² = 21.4
p = .002
0 1 2 3 4 5 6
Reading Problem Score

B

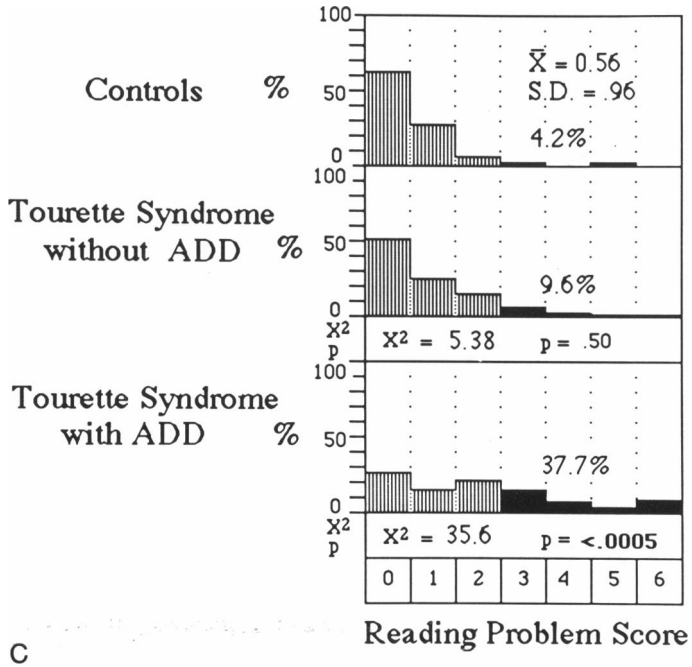
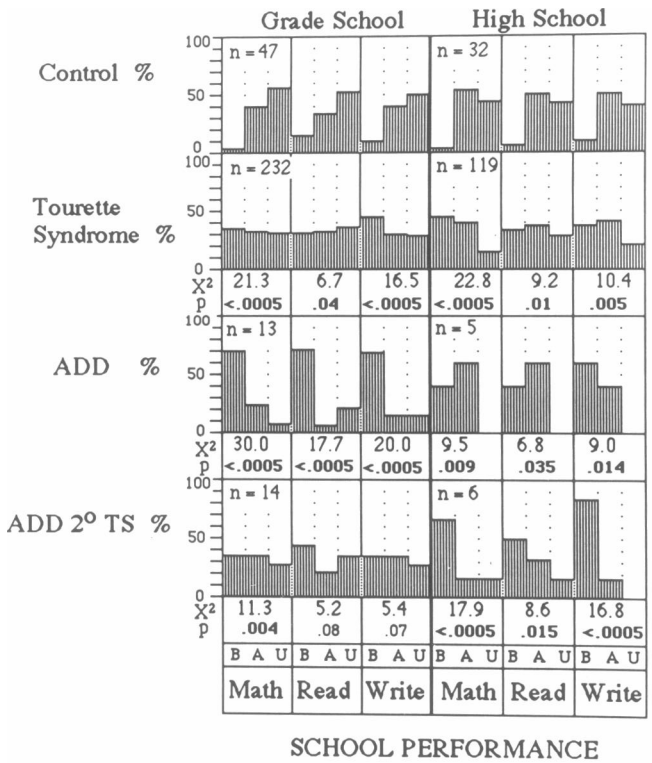


FIG. 7.—Reading-problem score in (*A*) controls, TS, ADD, and ADD 2^0 TS groups, (*B*) controls and the three grades of TS, and (*C*) controls, TS without ADD and TS with ADD. The mean ± SD of the reading score for each group is given. The scores ≥3 are in black, and the percentage of individuals with such scores is given. The significant *P* values for χ^2 tests are boldface.



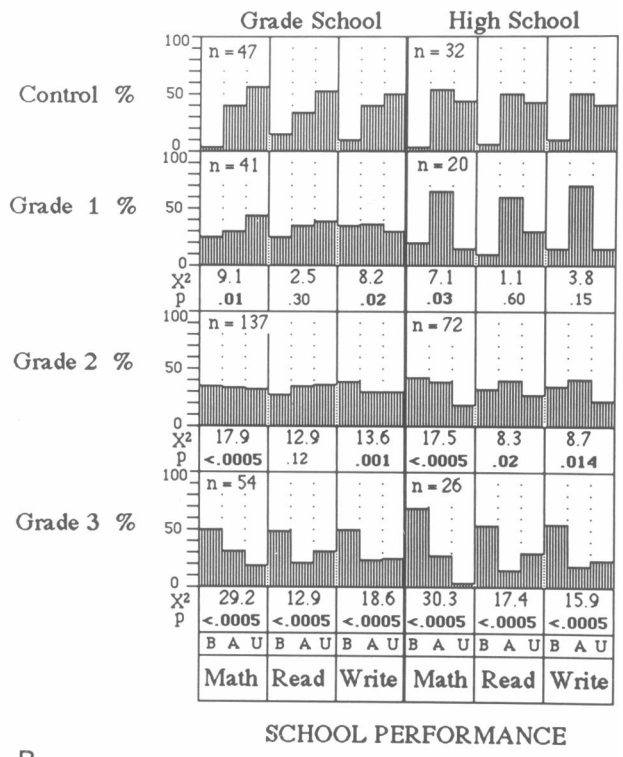


FIG. 8.—School performance in grade school and high school for (*A*) control, TS, ADD, and ADD 2° TS groups and (*B*) controls and the three grades of TS. The number of patients in the appropriate age range is given. B = Below average; A = average; and U = above average.

those for TS patients, although the numbers are small. The ADD 2^0 TS patients also had the greatest problems in math. In all three grades of TS, math performance was also significantly poorer than that in controls. For grade 3 TS, the performance was poorer at $P < .0005$ for all three categories, both in grade school and in high school (fig. 8*B*).

School Problems

School is a problem for many children with TS. The Appendix summarizes the different areas that impact on TS patients to cause school problems. Motor tics, especially if they are severe, cause three types of problems. First, they may interfere with reading or writing. Rapid eye-blinking, eye-gazing, and head-jerking tics can be so severe as to make it difficult for the children to keep their eyes on the page. Second, such tics may result in ridicule by the student's peers. This can particularly cause trouble if leg tics affect walking, such that the student is labeled "weird" or a "fairy." Third, teachers may misinterpret the tics as deliberate misbehavior and discipline the students for actions that they cannot control. Vocal tics cause a similar set of problems. Teachers often think that such noises are attention-seeking or deliberate acting-out misbehavior. The ADD present in two-thirds of TS patients (Comings and Comings 1984, 1985) presents all the problems that are well known to be associated with this disorder.

The learning and reading problems of TS patients have been documented above. If we take a reading-problem score of ≥ 3 as an indicator of dyslexia-like problems, then 27% of TS patients have some problems with dyslexia. Poor retention of material that was read was considered to be a problem in 41% of TS patients, compared with 8.3% of controls. Our finding of reading problems (defined as a reading-problem score of ≥ 3 or more) in 4% of controls agrees well with the results of other studies. In an epidemiological study of specific reading retardation, Berger et al. (1975) found that 3.9% of 10-year-olds on the Isle of Wight and 9.9% of children in an inner London borough had some sort of reading disability. Badian (1984) reported that 4% of 8–12-year-olds in Boston had a reading disability, despite having IQs ≥ 85. There is an increased prevalence of reading disability in males, with a male:female ratio of 3.5:1 (Hier and Kaplan 1980). These findings indicate that reading problems are six to seven times more common in TS patients than in the general population.

Because of their uncontrollable, intrusive nature, obsessive thoughts can cause severe problems in reading. Many patients, including adults, complain that their thoughts race so fast that they cannot latch onto a single train of thought. Compulsive behaviors can be particularly troublesome. The need to compulsively start again at the beginning of a sentence, repeat a word, count words in a sentence, erase errors until there is a hole in the paper, or arrange and rearrange papers on the desk until they are in just the right order are some of the typical compulsions that interfere with schoolwork. Various types of phobias and panic attacks are also common in TS, as discussed in Part III (Comings and Comings 1987*b*). In grade-school children these may manifest as school phobia. This may be present in children who are not on medication or

may be precipitated or exacerbated by haldol (Mikkelsen et al. 1981). A variety of other phobias may contribute to the primary school phobia. Related to the propensity for panic attacks (Comings and Comings 1987*b*) is the significantly increased frequency of test anxiety (see above).

Echolalia and paralalia may be misinterpreted as attention-getting behavior. Perseveration—the tendency to ask the same question over and over, even though the child knows the answer—can be particularly irritating to teachers and parents who do not understand that it is a common symptom in TS. In addition to primary school and learning problems, many of the ancillary symptoms of TS can lead to such severe socialization problems that simple lack of friends contributes to school being an unrewarding experience. Short temper, coprolalia, and copropraxia can cause obvious problems. Excessive, compulsive touching of other children, especially sexual touching, can severely interfere with normal social interactions. This, along with a frequent fear of abandonment, can result in a TS child being such a clinging vine that his peers counterreact by rejecting him. A tendency toward exhibitionism in some patients may lead to ridicule and ostracism.

In addition to these symptoms, there can also be a primary problem with socialization, one that seems to be related to the learning disorder—e.g., trouble simply learning how to interact with others and learning how to pick up and retain the often subtle signals about what is appropriate and what is inappropriate behavior. There is also frequently a tendency for TS patients to fail to accept responsibility for their own actions, to blame others for all their problems, and to rigidly want everything done their way. All of the above can lead to rejection and poor self-esteem.

Haloperidol and pimozide, both phenothiazine-type medications, can cause cognitive blunting and contribute to learning problems. It is critical to keep the doses of these medications at the lowest level consistent with control of 70%–90% of the tics.

Management of School Problems

Once the tics and vocal noises have been brought under control, much time in the management of TS patients is concerned with managing problems in school and behavior at home. Treatment of the behavior problems is discussed in Part II (Comings and Comings 1987*a*). The following are some of the approaches that help in management of the school problems:

1. *Proper diagnosis.*—This may seem self-evident, but it is the most important first step. If the parents, teachers, patients, and physicians are not aware of what they are dealing with, none of the following steps are possible. Many patients have needlessly struggled through years of problems because of no diagnosis or an incorrect diagnosis. SED, ADDH, conduct disorder, childhood schizophrenia, aphasia, and autism are the most common prior diagnoses. Aspects of each of these may be present, but the primary diagnosis is TS.

2. *Treatment of the ADD.*—Since a significant proportion of the school problems are related to the ADD present in the majority of TS patients, appropriate medical and school treatment of this aspect is important.

3. *Education of teachers and peers.*—Much of the misunderstanding of teachers and ridicule by peers can be thwarted by educating them about TS. Appropriate pamphlets from the Tourette Syndrome Association (42–40 Bell Blvd., Bayside, NY 11361-2857) are very helpful for teachers. Inservices to educate teachers and school psychologists about TS are extremely helpful. A side effect of this is that over the subsequent years many new cases of TS are often recognized by teachers who have attended such inservices. Classroom discussion with the students or presentation of videotapes transfers the onus to the peers if they choose to continue to ridicule the TS patient. We have seen many cases in which the teasing by peers has immediately ceased following such presentations.

4. *Tutors.*—Since some of the learning problems can be solved by additional, one-on-one help, the hiring of a tutor for 1–3 h/wk is adequate for many TS patients.

5. *Individual education programs (IEPs).*—If a tutor alone is not adequate, obtaining an IEP is a critical first step in providing some of the special approaches required for the education of TS children (see Federal Law 94-142). One or more of the following may be included in the IEP, depending on the needs of the individual patient:

a. Reduction of noise. Both as a part of the ADDH and of the TS itself, background noises tend to be particularly distracting. Placement of TS patients in special smaller classes often alleviates this problem.

b. Modification of timed tests. Because of the dyslexia symptoms, slow reading, poor retention, and test anxiety, timed tests are often a special problem for some TS patients. Rigid requirements for advancement based on passing such tests should be modified or eliminated.

c. Presentation of material in small blocks. An entire page of math problems of printed material can often throw a TS patient into panic. Presentation of the same material in small segments can alleviate this problem.

d. Reduction of work load. A simple reduction of the work load may significantly reduce the stress on the child. This can change a child who hates school into one who enjoys it. We have also seen it significantly reduce the number of tics.

e. Alternative inputs of information. For those with particularly severe dyslexia, the input of information via audiotape, as is used for blind children, may bypass the reading problems. Also, the early use of calculators may allow students who are having great difficulties memorizing multiplication tables to still appreciate the fun of mathematics.

f. Special classes. Most TS children who get placed in special EH or LH classes find themselves with other children having ADDH. Since this is one of the major secondary diagnoses in TS, such placement is often the most appropriate of several alternatives and far more appropriate than placement in classes for the orthopedically handicapped. The latter type of class tends to further stigmatize the TS child as different from his peers. Resource classes for work on special problems are an intermediate solution between tutoring and full-time special classes. The special class should provide the increased struc-

ture that the TS child requires yet not be so regimented that the child cannot work out his or her tics and motor hyperactivity. A TS-and-ADD child should not be required or expected either to sit still or to stay seated for long periods of time.

g. Psychological testing. Psychological testing is the first step utilized by most school districts in the evaluation of a child pinpointed by parents or teachers as having problems. Although such testing is important, the results may work against the student in the following two seemingly opposite ways in different patients:

1. Underestimation of potential. Because of problems with ADD, dyslexia, or retention of information, IQ testing may underestimate the true intellectual potential of a TS student, with the result that expectations are unrealistically low.

2. Overestimation of potential. In the opposite direction, since most testing is done in a quiet room with one-on-one interaction, it may fail to detect the significant deterioration of performance that occurs when the TS-and-ADD child is attempting to function in a large, noisy classroom. As a result, the parents are aware of the fact that their child is performing far below his or her true potential, but attempts to get placement in special classes is thwarted by the testing, which indicates that the child is not 2 years behind the norm. As a result, the parents and the school often end up in a constant adversarial relationship. The final resolution depends on the persistence of the parents, the education of the school about the special problems of TS children, and obtaining a satisfactory IEP.

h. Time-out areas. As discussed in Part III, some TS children have temper tantrums or emotionally loose control. Placing the child in a time-out area, in a nonpunitive fashion, will help to allow the child to regain his or her composure.

6. *Psychotherapy.*—The problems with behavioral and socialization skills often require family or individual psychotherapy. These problems are discussed in Part II (Comings and Comings 1987*a*).

TS and the Genetics of Dyslexia

Many studies have been reported on the genetics of dyslexia and various specific reading and learning disabilities (Hallgren 1950; Zahalkova et al. 1972; Finucci et al. 1976; Herschel 1978; Omenn and Weber 1978; Finucci and Childs 1983). Zahalkova et al. (1972) concluded that dyslexia was inherited as an autosomal dominant trait with reduced penetrance in females. Finucci et al. (1976) found that 45% of first-degree relatives of dyslexics had a reading disability. At an estimated population frequency of 2%–5%, dyslexia is most likely multifactorial in origin. The involvement of at least two genes has been shown by Smith et al. (in press), who have shown that one-third of their dyslexic families showed linkage to a heterochromatic marker on chromosome 15. A *TS* gene appears to be one of several genes causing dyslexia. Our linkage studies have ruled out linkage of *TS* to the centromere of chromosome 15 (Comings et al. 1987*a*, 1987*b*). In the present study 26.8% of TS patients had a reading-

problem score ≥3, compared with 4.2% of the controls. We have frequently observed families in which first-degree relatives of TS probands had significant reading disabilities but no tics or vocal noises. These individuals may present dyslexia alone as a partial expression of the *TS* gene.

TS and the Genetics of Stuttering

In a genetic study of stuttering, Kidd and Records (1982) concluded that most if not all of the transmission of stuttering is genetic. There was a 3:1 male:female ratio, and 22% of male first-degree relatives and 7.5% of female first-degree relatives also stuttered, compared with a 3%–5% frequency for males and a 1%–2% frequency for females in the general population. They found that both a multifactorial/polygenic and a single-major-locus model fit the segregation data. The finding of the present study—i.e., that 31% of TS patients have had problems with stuttering, compared with 6.25% of the controls—indicates that the *TS* gene is one of the single major loci causing stuttering. If we assume that 1.2% of the population carry a *TS* gene (Comings et al. 1984; Devor 1984; Pauls and Leckman 1986), that 30% of these have problems with stuttering, and that *TS*-gene carriers without motor or vocal tics can express the gene as isolated stuttering, then ~0.4% of the population may have problems with stuttering due to a *TS* gene. This figure suggests that between 10% and 20% of stuttering may be due to a *TS* gene. In this regard, it is of interest that haloperidol has often been shown to be an effective drug in the treatment of some cases of stuttering (Tapia 1969; Wells and Malcolm 1971; Quinn and Peachy 1973; Burnes et al. 1978).

APPENDIX

CAUSES OF SCHOOL PROBLEMS IN TS

I. Primary TS symptoms
   A. Motor tics
   B. Vocal tics
II. ADD/H
III. Learning disorders
   A. Dyslexia
   B. Poor retention
IV. Obsessive-compulsive behaviors
   A. Obsessive thoughts
   B. Racing thoughts
   C. Compulsive behaviors
V. Phobias and panic attacks
   A. Primary school phobia
   B. Other phobias
   C. Test anxiety
VI. Other secondary symptoms
   A. Echolalia and paralalia
   B. Short temper
   C. Coprolalia and copropraxia

D. Excessive touching and sexual touching
E. Exhibitionism
VII. Poor socialization skills
VIII. Poor self-esteem
IX. Medication

REFERENCES

Bachman, D. S. 1981. Pemoline-induced Tourette's disorder: a case report. Am. J. Psychiatry **138**:1116–1117.

Badian, N. A. 1984. Reading disability in an epidemiological context: incidence and environmental correlates. J. Reading Disabilities **17**:129–136.

Baron, M., E. Shapiro, A. Shapiro, and J. D. Rainer. 1981. Genetic analysis of Tourette syndrome suggesting major gene effect. Am. J. Hum. Genet. **33**:767–775.

Berger, M., W. Yule, and M. Rutter. 1975. Attainment and adjustment in two geographical areas. II. The prevalence of specific reading retardation. Br. J. Psychiatry **126**: 510–519.

Bornstein, R. A., G. King, and A. Carroll. 1983. Neuropsychological abnormalities in Gilles de la Tourette syndrome. J. Nerv. Ment. Dis. **171**:497–502.

Bremness, A. B., and J. Sverd. 1979. Methylphenidate-induced Tourette syndrome: case report. Am. J. Psychiatry **136**:1334–1335.

Burnes, D., J. P. Brady, and K. Kurvilla. 1978. The acute effect of haloperidol and apomorphine on the severity of stuttering. Biol. Psychiatry **13**:255–264.

Cadoret, R. J., L. Cunningham, R. Loftus, and J. Edwards. 1975. Studies of adoptees from psychiatrically disturbed biological parents. II. Temperment, hyperactive, antisocial, and developmental variables. J. Pediatr. **87**:301–306.

Cantwell, D. P. Genetic factors in hyperkinetic syndrome. 1976. J. Am. Acad. Child Psychiatry **15**:214–223.

Cohen, D. J., J. Detlor, B. A. Shaywitz, and J. F. Leckman. 1982. Interaction of biological and psychological factors in the natural history of Tourette syndrome: a paradigm for childhood neuropsychiatric disorders. Pp. 31–40 *in* A. J. Friedhoff and T. N. Chase, eds. Gilles de la Tourette syndrome. Raven, New York.

Cohen, D. J., J. F. Leckman, and B. A. Shaywitz. 1983. Tourette's syndrome and other tics. Pp. 3–28 *in* D. Shaffer, A. A. Ehrhardt, and L. Greenhill, eds. A clinical guide to child psychiatry. MacMillan Free, New York.

Comings, D. E. 1987. A controlled study of Tourette syndrome. VII. Summary: a common genetic disorder causing disinhibition of the limbic system. Am. J. Hum. Genet. **41**:839–866.

Comings, D. E., and B. G. Comings. 1982. Familial exhibitionism in Gilles de la Tourette syndrome successfully treated with haloperidol. Am. J. Psychiatry **139**:913–915.

———. 1984. Tourette's syndrome and attention deficit disorder with hyperactivity: are they genetically related? J. Am. Acad. Child Psychiatry **23**:138–146.

———. 1985. Tourette syndrome: clinical and psychological aspects of 250 cases. Am. J. Hum. Genet. **37**:435–450.

———. 1986. Evidence for an X-linked modifier gene affecting the expression of Tourette syndrome and its relevance to the increased frequency of speech, cognitive and behavioral disorders in males. Proc. Natl. Acad. Sci. USA **83**:2551–2555.

———. 1987*a*. A controlled study of Tourette syndrome. II. Conduct. Am. J. Hum. Genet. **41**:742–760.

———. 1987*b*. A controlled study of Tourette syndrome. III. Phobias and panic attacks. Am. J. Hum. Genet. **41**:761–781.

———. 1987*c*. Hereditary agoraphobia with panic attacks and hereditary obsessive-

compulsive behavior in relatives of patients with Tourette syndrome. Br. J. Psychiatry **148** (in press).

———. Tourette syndrome and ADD (letter to the editor). Arch. Gen. Psychiatry (in press).

Comings, D. E., B. G. Comings, E. J. Devor, and C. R. Cloninger. 1984. Detection of major gene for Gilles de la Tourette syndrome. Am. J. Hum. Genet. **36**:586–600.

Comings, D. E., B. G. Comings, G. Dietz, D. Muhleman, T. A. Okada, F. Sarinana, R. Simmer, R. Sparkes, M. Crist, and D. Stock. 1986*a*. Linkage studies in Tourette syndrome. Am. J. Hum. Genet. **39**:A151.

Comings, D. E., B. G. Comings, G. Dietz, D. Muhleman, T. A. Okada, F. Sarinana, R. Simmer, and D. Stock. 1986*b*. Evidence the Tourette syndrome gene is at 18q22.1 (abstract). P. 620 *in* 7th International Congress of Human Genetics, Berlin, Sept 22–26.

Devor, E. J. 1984. Complex segregation analysis of Gilles de la Tourette syndrome: further evidence for a major locus mode of transmission. Am. J. Hum. Genet. **36**:704–709.

Diagnostic and statistical manual of mental disorders. 3d ed. (DSM III). 1980. American Psychiatric Association, Washington, D.C.

Eldridge, R., R. Sweet, C. R. Lake, M. Ziegler, and A. K. Shapiro. 1977. Gilles de la Tourette's syndrome: clinical, genetic, psychologic, and biochemical aspects in 21 selected families. Neurology **27**:115–124.

Finucci, J. A., and B. Childs. 1983. Dyslexia: family studies. Pp. 157–167 *in* C. L. Ludlow and J. A. Cooper, eds. Genetic aspects of speech and language disorders. Academic Press, New York.

Finucci, J. M., J. T. Guthrie, A. L. Childs, H. Abbey, and B. Childs. 1976. The genetics of specific reading disability. Ann. Hum. Genet. **40**:1–23.

Friedhoff, A. J., and T. N. Chase, eds. 1982. Gilles de la Tourette syndrome. Raven, New York.

Golden, G. S. 1974. Gilles de la Tourette's syndrome following methylphenidate administration. Dev. Med. Child Neurol. **16**:76–78.

———. 1978. Tics and Tourette's: a continuum of symptoms? Ann. Neurol. **4**:145–148.

Hagin, R. A., R. Beecher, G. Pagano, and H. Kreeger. 1982. Effects of Tourette syndrome on learning. Pp. 323–328 *in* A. J. Friedhoff and T. N. Chase, eds. Gilles de la Tourette syndrome. Raven, New York.

Hallgren, B. 1950. Specific dyslexia: a clinical and genetic study. Acta Psychiatr. Neurol. Scand. [Suppl.] **65**:1–287.

Herschel. M. 1978. Dyslexia revisited. Hum. Genet. **40**:115–134.

Hier, D. B., and J. Kaplan. 1980. Are sex differences in cerebral organization clinically significant? Behav. Brain Sci. **3**:238–239.

Jackson, D. M., N.-B. Anden, and A. Dahlstrom. 1975. A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. Psychopharmacologia **45**:139–149.

Kidd, K. K., B. A. Prusoff, and D. J. Cohen. 1980. Familial pattern of Gilles de la Tourette syndrome. Arch. Gen. Psychiatry **37**:1336–1339.

Kidd, K. K., and M. A. Records. 1982. Genetic methodologies for the study of speech. Pp. 311–343 *in* X. O. Breakfield, ed. Neurogenetics: genetic approaches to the nervous system. Elsevier, New York.

Lowe, T. L., D. J. Cohen, J. Detlor, M. W. Kremenitzer, and B. A. Shaywitz. 1982. Stimulant medications precipitate Tourette's syndrome. JAMA **247**:1729–1731.

Lucas, A. R., P. E. Kauffman, and E. M. Morris. 1967. Gilles de la Tourette disease: control of symptoms and its clinical course. Int. J. Neuropsychiatry **3**:96–109.

Merali, Z., S. Johnston, and S. Zlacman. 1983. Bombesin-induced behavioral changes: antagonism by neuroleptics. Peptide **4**:693–697.

Mikkelsen, E. J., J. Detlor, and D. J. Cohen. 1981. School avoidance and social phobia

triggered by haloperidol in patients with Tourette's disorder. Am. J. Psychiatry **138**:1572–1576.

Morrison, J. R., and M. A. Stewart. 1971. A family study of the hyperkinetic child syndrome. Biol. Psychiatry **3**:189–195.

———. 1974. Bilateral inheritance as evidence for polygenicity in the hyperactive child syndrome. J. Nerv. Ment. Dis. **158**:226–228.

Nee, L. E., E. D. Caine, R. J. Polinsky, R. Eldridge, and M. H. Ebert. 1980. Gilles de la Tourette syndrome: clinical and family study in 50 cases. Ann. Neurol. **7**:41–49.

Omenn, G. S., and B. A. Weber. 1978. Dyslexia: search for phenotypic and genetic heterogeneity. Am. J. Med. Genet. **1**:333–342.

Parker, K. 1985. Helping school-age children cope with Tourette syndrome. J. School Health **55**:30–32.

Pauls, D. L., D. J. Cohen, R. Meimbuch, J. Detlor, and K. K. Kidd. 1981. Familial pattern and transmission of Gilles de la Tourette syndrome and multiple tics. Arch. Gen. Psychiatry **38**:1091–1093.

Pauls, D. L., C. R. Hurst, K. K. Kidd, S. D. Kruger, J. F. Leckman, and D. J. Cohen. 1986. Gilles de la Tourette's syndrome and attention deficit disorder with hyperactivity: evidence against a genetic relationship. Arch. Gen. Psychiatry **43**:1177–1179.

Pauls, D. L., and J. F. Leckman. 1986. The inheritance of Gilles de la Tourette syndrome and associated behaviors: evidence for autosomal dominant transmission. N. Engl. J. Med. **315**:993–997.

Pert, A., T. W. Moody, C. B. Pert, L. A. Dewald, and J. Rivier. 1980. Bombesin: receptor distribution in brain and effects on nociception and locomotor activity. Brain Res. **193**:209–220.

Pollack, M. A., N. L. Cohen, and A. J. Friedhoff. 1977. Gilles de la Tourette's syndrome: familial occurrence and precipitation by methylphenidate therapy. Arch. Neurol. **34**:630–632.

Price, R. A., J. F. Leckman, D. L. Pauls, D. J. Cohen, and K. K. Kidd. 1986. Gilles de la Tourette's syndrome: tics and central nervous system stimulants in twins and nontwins. Neurology **36**:232–237.

Quinn, A. N., and R. J. Thompson, Jr. 1980. Tourette's syndrome: an expanded view. Pediatrics **66**:420–424.

Quinn, P. T., and E. C. Peachy. 1973. Haloperidol in the treatment of stutterers (letter). Br. J. Psychiatry **123**:247–255.

Robins, L. N., J. E. Helzer, J. Croughan, and K. S. Ratclif. 1981. National Institute of Mental Health diagnostic interview schedule. Arch. Gen. Psychiatry **38**:381–389.

Schultz, D. W., P. W. Kalivas, C. B. Memeroff, and A. J. Prange. 1984. Bombesin-induced locomotor hyperactivity: evaluation of the involvement of the mesolimbic dopamine system. Brain Res. **304**:377–382.

Shafer, D. 1973. A familial factor in minimal brain dysfunction. Behav. Genet. **3**:175–186.

Shapiro, A. K., and E. S. Shapiro. 1981. Do stimulants provoke, cause, or exacerbate tics and Tourette syndrome? Comp. Psychiatry **22**:265–273.

Shapiro, A. K., E. S. Shapiro, R. D. Bruun, and R. D. Sweet. 1978. Gilles de la Tourette syndrome. Raven, New York.

Shapiro, A. K., E. S. Shapiro, H. L. Wayne, and J. Clarkin. 1973. Organic factors in Gilles de la Tourette's syndrome. Br. J. Psychiatry **122**:659–664.

Sleator, E. K. 1980. Deleterious effects of drugs used for hyperactivity on patients with Gilles de la Tourette syndrome. Clin. Pediatr. **19**:452–454.

Smith, S. D., B. F. Pennington, W. J. Kimberling, P. R. Fain, P. S. Ing, and H. A. Lubs. 1987. Genetic heterogeneity in specific reading disability. Am. J. Hum. Genet. **39**(Suppl.): A169.

Stefl, M. E., and M. Rubin. 1985. Tourette syndrome in the classroom: special problems, special needs. J. School Health **55**:72–75.

Sutherland, R. J., B. Kold, W. M. Schoel, I. Q. Whishaw, and D. Davies. 1982. Neuropsychological assessment of children and adults with Tourette syndrome: a comparison with learning disabilities and schizophrenia. Pp. 311–322 *in* A. J. Friedhoff and T. N. Chase, eds. Gilles de la Tourette syndrome. Raven, New York.

Tapia, F. 1969. Haldol in the treatment of children with tics and stutterers—and an incidental finding. Psychiatr. Q. **43**:647–649.

Wells, P. G., and M. T. Malcolm. 1971. Controlled trial of treatment of 36 stutterers. Br. J. Psychiatry **119**:603–604.

Welner, Z., A. Welner, M. Stewart, H. Palkes, and E. Wish. 1977. A controlled study of siblings of hyperactive children. J. Nerv. Ment. Dis. **165**:110–117.

Zahalkova, M., V. Vrzal, and E. Kloboukova. 1972. Genetical investigations in dyslexia. J. Med. Genet. **9**:48–52.