PSYCHIATRIC FAMILY HISTORY AND NEUROLOGICAL DISEASE IN AUTISTIC SPECTRUM DISORDERS

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The etiology of infantile autism is obscure, for several reasons. First, the manifestations of autism are complex, and include cognitive, affective and even motor elements. Second, the range of severity of autistic manifestations is extremely wide, raising the question of whether low-functioning and high-functioning individuals indeed have common attributes. This has led some authors to separate Asperger syndrome from autism, while many would equate it with high-functioning autism (Cox 1991). Gillberg (1990), recognizing a continuity throughout the range of autism, introduced the concept of autistic spectrum disorders (ASD). Finally, autism may occur with neurological disorders (symptomatic autism) or without an evident neurological substrate (idiopathic autism). Some studies (*e.g.* Garreau *et al.* 1984) have suggested that the behavioral features are the same in both. However, those with neurological disease are more often low-functioning (DeLong and Dwyer 1988).

Despite the severe affective disturbances seen in autism, reports of an association between autism (or Asperger syndrome) and affective disorder have only recently appeared in the literature. Gillberg (1985) published a case of Asperger syndrome with recurrent psychosis, with a family history of manic-depressive psychosis. Wing (1981) followed a group of patients with Asperger syndrome through adolescence, and found that nearly half developed affective disorders. Steingard and Biederman (1987) reported two autistic individuals with manic-like symptoms responsive to lithium. Komoto *et al.* (1984) described three case studies of autistic children who also had affective disorder and family histories of depression and manic depression. These patients showed 'periodicity' or 'cyclicity' of autistic symptoms, which we have also observed (unpublished observations). DeLong and Aldershof (1988) found high rates of manic depression in the families of children with autism or pervasive developmental disorder with special abilities. DeLong and Dwyer (1988) surveyed relatives of probands with autism; the incidence of manic depression among the relatives was 4·2 per cent (about five times greater than that expected in the general population, according to Robins *et al.* 1984), and was higher among relatives of probands with Asperger syndrome (6·1 per cent *vs.* 3·3 per cent, $p<0·05$). Gillberg (1989) found family histories of major affective disorder in four of 23 children with Asperger syndrome (and in 13 per cent of all those with autism). Piven *et al.* (1991) reported that the lifetime prevalence rate of major depressive disorder may be high in the

parents of autistic probands (27 per cent) in comparison with population norms, but found no increase in bipolar disease.

The present study reports on a clinically accrued group of children with autistic spectrum disorders (ASD) investigated for neurological disease and familial psychopathology, particularly major affective disorder.

Method

Subjects

The study group comprised all of the 40 children and adolescents with autistic spectrum disorders evaluated by the authors during a four-year period in the Pediatric Neurology Division at Duke University Medical Center. We used the DSM-III-R criteria of the American Psychiatric Association (1987) to diagnose autism and pervasive developmental disorder (not otherwise specified). Asperger syndrome was diagnosed according to the clinical criteria given by Wing (1981). 33 of the 40 had been diagnosed independently before referral, most by the TEACCH program for autistic children of the state of North Carolina using the Childhood Autism Rating Scale (CARS) (Schopler *et al.* 1986), but some by other developmental evaluation units; our diagnosis agreed with the referral diagnosis in every such case.

The group represents referrals to the clinic, and was not a population-based or other epidemiological sample. Any bias caused by referral to a child neurologist would presumably be in the direction of over-representation of 'neurological' cases. 34 were male; the characteristics of the six females are given separately in Table V. The mean age of the group was eight years. Three were diagnosed as having pervasive developmental disorder (not otherwise specified), four as having Asperger syndrome, and the rest as having autism. Seven had a WISC-R Verbal IQ of over 70. Of 20 with identifiable neurological disorder, all had a WISC-R Verbal IQ of under 50, and 12 were non-verbal. Eight of the 40 were black, the rest caucasian.

Evaluation

The study was clinically based; the individuals were evaluated and followed by the author. The patients were evaluated extensively for neurological etiology, with neurological examinations, EEG, biochemical studies, CT, MRI, $F^{18}DG$ positron emission tomography and karyotyping as indicated. Only summary results of the neurological findings are presented, since the focus of this paper is on the relative proportion of neurological and idiopathic cases, and the incidence of major affective disorder in the families of individuals with neurological and idiopathic ASD. Features of the neurological evaluations will be published separately.

The family histories were obtained from parents and other family members in repeated clinical interviews by the authors. The first author (R.D.) asked for information about family history in the first interview and during all subsequent encounters. Several months later, the second author (C.N.) contacted families by telephone or in person to review and complete the family history data. 52 relatives were interviewed—mainly mothers and fathers, but also aunts and grandmothers. At least one relative was interviewed from each family except one, in which the mother, maternal grandmother, and mother's two brothers had all been diagnosed as being manic-depressive, had extensive histories of hospitalization, were not caring for the child and were unavailable for interview. The history, obtained from case workers, is nevertheless considered very reliable. Seven of the affected relatives, primarily mothers of the subjects, were interviewed; diagnoses in the others were made on the basis of their histories, obtained from family members. In all, 420 relatives were surveyed. The family history study included three generations (siblings, parents, parents' siblings, grandparents and cousins; grandparents' siblings were considered separately).

At the time of the first interview, and at the late contacts with the families, the interviewer did not know the child's diagnosis; neurological diagnoses generally were not made until after testing was complete, and the second author did not know the neurological diagnoses of the probands. The neuropsychiatric diagnoses were recorded according to the Family History Research Diagnostic Criteria

(Andreasen *et al.* 1977), which are similar to those of the DSM-III-R (American Psychiatric Association 1987). In addition to descriptive criteria, note was made of specific facts, including history of psychiatric hospitalization, specific diagnosis given by a psychiatrist, use of psychotropic medication (especially lithium), suicide or attempted suicide, 'nervous breakdown', postpartum psychosis, *etc.* One or more of these facts were required before a diagnosis was attributed to a relative.

The family history method has been shown to have high specificity and low sensitivity (Thompson *et al.* 1982); it also has greater accuracy for major psychiatric illnesses, especially major affective disorders (bipolar disorder and major depression)—*i.e.* the illnesses most pertinent to the present study. The longitudinal clinical approach, using repeated interviews over time, probably increased the sensitivity and specificity of the findings. Important family history information often emerged only after repeated contact with the patient's family. Only major affective disorders (bipolar disorder and major depression) were analysed; other familial psychiatric and cognitive findings for a similar sample have been reported previously (DeLong and Dwyer 1988), but are noted here for completeness (see Table II). We have no specific information concerning the age at onset of the psychiatric illness in affected relatives.

This study uses the concept of ASD (Gillberg 1990), accepting that it includes autistic disorder (DSM-III-R), Asperger syndrome (defined according to the clinical description of Wing 1981), and pervasive developmental disorder, not otherwise specified (DSM-III-R). DSM-III-R recognizes autistic disorder as the only subgroup of the general category pervasive developmental disorder (PDD), and considers autistic disorder to be the most severe and prototypical form of PDD. PDD without prominent autistic features is not included in this study.

The level of cognitive ability was determined from clinical observation and the most recent psychometric data for each individual. Morbid risks are reported as uncorrected percentages. Statistical correlations were determined by χ^2 analysis using Yates' correction.

TABLE I
Neurological diagnoses in probands with autism (N = 20)

Diagnosis	*N*
Congenital rubella	1
Fragile X syndrome	1
Tuberous sclerosis	1
Post-encephalitic epilepsy	2
Ring chromosome	1
Cerebral cortical dysgenesis	3
Brain malformation with hydrocephalus	3
Undiagnosed encephalopathy with epilepsy	8

Results

Of the 40 probands evaluated, 20 had identifiable neurological disorders which could account for their autism (Table I). As noted, all of these patients had a diagnosis of autism; all were low-functioning and 12 were non-verbal. The other 20 probands had no identifiable neurological disorder which could account for their autistic spectrum disorder; this group overall was higher-functioning, and included three individuals diagnosed as having PDD, four as having Asperger syndrome and 13 as having autism.

The summary findings of the familial psychiatric histories of those probands with neurological disorders and those without are as follows. Of the 20 individuals with neurological disorders, 18 had a negative family history of major affective disorder. In contrast, of the 20 individuals with ASD but without neurological disorder, 14 had a positive family history of major affective disorder. Two probands with neurological disorder had a positive family history, and six had neither an identifiable neurological disorder nor a positive family history. This difference between the groups is highly significant ($\chi^2 = 12{\cdot}5$, $p < 0{\cdot}001$).

Only key features of the family history data (Table II) will be noted here. The 14 probands with a positive family history and no neurological diagnosis included 10 who had a family member diagnosed as having bipolar disorder. Overall, among these 14 families, 14 of 123 relatives surveyed had bipolar disorder (11·4 per cent), and an additional 19 (15·4 per cent)

TABLE II
Family history data

	FH pos., neu. neg.[1]	*FH pos., neu. pos.*	*FH neg., neu. neg.*	*FH neg., neu. pos.*	*Total*
Families (N)	14 (10 bipolar)	2	6	18	40
Relatives (N)	123	56	42	199	420
Bipolar disorder (N)	14 (11·4%)	0	0	0	14
Unipolar disorder (N)	19 (15·4%)	4 (7·1%)	0	0	23
Total with major affective disorder	33 (26·8%)	4 (7·1%)	0	0	37
Other psychiatric disorder	14* (11·4%)	2** (3·4%)	7† (16.7%)	15‡ (7·5%)	38
Major affective disease in parent	10 (35·7%)	0	0	0	10
In father	3 (1 bipolar, 2 unipolar)				
In mother	7 (2 bipolar, 5 unipolar)				

[1]FH pos./neg. family history present/absent; Neu. pos./neg. = neurological disorder present/absent.
*Learning disability (2), panic disorder (1), 'unstable' (1), 'mood swings' (1), antisocial personality (4), aggressive (1), attention deficit hyperactivity disorder (ADHD) (2), alcoholic (1), slow (1).
**Pervasive developmental disorder (1), alcoholic (1).
†'Dull' (4), mentally retarded (1), alcoholic (2).
‡'Slow' (2), mentally retarded (1), ADHD (1), antisocial personality (2), 'unstable' (3), alcoholic (6).

TABLE III
Diagnoses of probands with autistic spectrum disorder

	*FH pos., neu. neg.**	*FH pos., neu. pos.*	*FH neg., neu. neg.*	*FH neg., neu. pos.*
Pervasive developmental disorder	3	—	—	—
Asperger syndrome	3	—	1	—
Autism	8	2	5	18

*See Table II for explanation of abbreviations.

had a history of unipolar depression. Thus in these families the overall percentage of relatives having major affective disorder was 33 of 123 (26·8 per cent). Seven mothers and three fathers of these 14 probands had major affective disorder. Three of the parents had bipolar disorder (two mothers, one father). In contrast, among the other three groups (26 families), 297 relatives were surveyed with only four instances of unipolar depression found (1·3 per cent), none among parents. Other neuropsychiatric diagnoses were nearly equivalent among the groups: with a positive family history for major affective disorder, the incidence of other psychiatric diagnoses was 16 of 179 (8·9 per cent); with a negative family history for major affective disorder, the incidence was 22 of 241 (9 per cent).

Among the 14 families with family history but no neurological disorder, major affective disorder was found only on the maternal side in seven, on the paternal side in three, and on both in four families.

Table III shows that the higher-functioning end of the autistic spectrum (PDD and Asperger syndrome) occurred almost entirely within the group with a family history of major affective disorder and no identifiable neurological disease.

Table IV presents the findings for the six females. All were low-functioning, and four had neurological diagnoses; two had positive family histories.

Discussion

This study was designed to test the questions: (1) whether high- and low-functioning autism represent a single

TABLE IV
Characteristics of female probands

Patient	*Family history*	*Neurological history*	*Diagnosis*	*Neurological disorder*
1		+	Autism	Ring chromosome
2	-	+	Autism	Seizures, encephalopathy
3		-	Autism	Idiopathic (one of twins)
4	-	+	Autism	Seizures, encephalopathy
5	+	-	Autism	Idiopathic
6	+	+	Autism	Seizures, ?congenital encephalopathy

entity differing only quantitatively, and (2) whether familial psychiatric disorders (particularly bipolar disorder and major depression) are significantly associated with autism or with a subgroup of ASD. The first question is raised by the striking clinical differences between low- and high-functioning autism, which have led some authors to distinguish Asperger syndrome as a distinct (high-functioning) entity (Wing 1981). The second question arises from anecdotal reports in the literature (see the introduction) linking affective disorder, particularly bipolar disorder, with autism; and from our earlier studies which found a notable incidence of bipolar affective disorder in families of some subgroups of children with autism, particularly those with Asperger syndrome (DeLong and Dwyer 1988) and those with special abilities (DeLong and Aldershof 1988). In addition, our long-standing interest in the neurological substrate of autism prompted the intensive neurological investigations. They will be reported fully elsewhere; for the present study, they served the purpose of achieving optimum delineation and classification of the autistic subgroups.

The major findings of this study were as follows:

(1) Half of the individuals with ASD had identifiable neurological disorders. This group was uniformly low-functioning; about two-thirds were non-verbal. Their families had a very low incidence of affective disorder (1·6 per cent).

(2) About one-third of the probands with autism had no identifiable neurological substrate, but had a strong family history of affective disorder, especially bipolar disorder. Thus the probands had either a high concentration of relatives with major affective disorder, or almost none. In affected families, there was a high incidence throughout the pedigrees. Other neuropsychiatric diagnoses were approximately equivalent between the various groups.

(3) The individuals with ASD and a family history of major affective disorder included the higher-functioning individuals of the autistic spectrum. Of the 14 individuals with a positive family history and no neurological disorder, three were diagnosed as having PDD, three as having Asperger syndrome, and eight as having autism. Among the other 26 individuals in the study, all except one were diagnosed as having autism.

The incidence of major affective disorder in the families with a family history but no neurological disorders tended to be higher than that found in the standard family studies of morbid risks of affective disorder in first-degree relatives of adult bipolar patients, and is accounted for by a higher incidence of bipolar disorder: Gershon *et al.* (1982) found 8·6 per cent, Coryell *et al.* (1985) 5·4 per cent, and Fieve *et al.* (1984) 5·1 per cent risk of bipolar disorder (compared with our finding of 11·4 per cent); and 14 per cent, 22·7 per cent and 6·4 per cent risk for unipolar disorders, respectively (*vs.* our 15·4 per cent). Gershon *et al.* (1982) found a total morbid risk of affective disorder of 24 per cent (including a small number with schizo-affective disorder), very similar to our findings (26·8 per cent). The morbid risk in the families of our subjects will in fact be higher, because

we included first cousins and grandparents, and because our patients and their families, particularly siblings and first cousins, were young and therefore below the major period of risk. The findings that these probands with ASD had an equal or greater familial risk than adult bipolar patients raises the question of whether the neuropsychiatric syndrome of these individuals represents a childhood manifestation of familial major affective disorder.

Patients with childhood-onset bipolar disorder have a higher morbid risk in relatives than those with adult-onset bipolar disorder. Dwyer and DeLong (1987), in a family history study of 20 probands with childhood-onset bipolar disorder, found an uncorrected incidence of 13 per cent for bipolar disorder among first-degree relatives, and of 27 per cent for unipolar depression. Strober *et al.* (1988) also found an increased morbid risk among first-degree relatives of probands with adolescent-onset bipolar disorder. Similarly, more severe disease may be associated with a higher morbid risk in families: Gershon *et al.* (1982) found that relatives of schizo-affective probands had a higher incidence of bipolar disorder (and of schizo-affective disease) than did relatives of probands with bipolar disorder. These observations suggest that a heavier familial genetic loading may result in earlier onset and greater severity of disease.

If this idea were extended to our patients with idiopathic ASD, the early onset of symptoms (in infancy or early childhood) and the severe manifestations (including cognitive as well as affective disorders) might be seen as a result of the extremely heavy familial loading. A family with a high incidence of bipolar disease might produce a child with autism or ASD as an extreme phenotypic manifestation of the genetic disorder, in the same way that it might produce an individual with schizo-affective disorder (Gershon *et al.* 1982). Certain phenomenological similarities between these two entities make such a result comprehensible.

Several factors give confidence in the findings of this study. It was based on a long-term clinical method, which aided discovery of information about family history. The sample of ASD was broadly representative. The family history surveys included three generations. The neurological cases, in particular, and the idiopathic cases with negative findings provided controls for the family history studies. They illustrate that the family histories, almost without exception, were either completely negative or densely positive.

The latter finding illustrates the importance of focusing on families rather than individuals in psychiatric studies of this kind. Our earlier study (DeLong and Dwyer 1988) diluted the salience of the family data by reporting the overall percentage of affected relatives from all autistic probands. Although that study involved an entirely different sample of patients (from Massachusetts rather than North Carolina) and was presented differently, findings were similar: 53 per cent of these patients had neurological abnormalities (*vs* 50 per cent in the present study); 4·2 per cent of all relatives surveyed had a history of bipolar disease (*vs* 3·3 per cent in the current study); and 12·2 per cent of all relatives had a history of major affective disorder (*vs* 8·8 per cent in the current study).

Other studies, besides those noted in the introduction, have found similar results to those reported here. Piven *et al.* (1990) found an increased incidence (15 per cent) of affective disease in adult siblings of individuals with autism. Subsequently they reported that the lifetime prevalence rate of major depressive disorder among parents of individuals with autism (27 per cent) may be high in comparison with population rates (Piven *et al.* 1991). In the latter study, however, of 81 parents of individuals with autism they found only one with manic depression. In the light of published familial data (*e.g.* Gershon *et al.* 1982), it is suprising to find an overall rate of major depression as high as 27 per cent without a significant admixture of bipolar disease. This difference between their findings and ours remains to be explained.

Lobascher *et al.* (1970) carried out a neurological and psychological study of 25 cases of infantile autism in Western Australia. They found 12 of the 25 to

have definite evidence of organic neurological disease, and found a family history of psychiatric illness (not further specified) in eight, alcoholism in eight, and mental retardation in six of the 23 families surveyed. Their findings that half (12/25) of the autistic children had evident neurological disease and one-third (8/23) had a family history of psychiatric illness are strikingly similar to the findings in the present study.

The findings of the present study, added to others in the literature, lead us to propose that an important subgroup of ASD may be related etiologically to familial major affective disorders (bipolar disorder and major depression), and may in fact represent the early-life onset of a severe phenotype of major affective, particularly bipolar, disease. This subgroup might be expected to have a distinctive clinical picture; detailed behavioral analysis, to be described elsewhere, suggests this may be so.

Accepted for publication 2nd September 1993.

Acknowledgements
We are grateful to many colleagues for contributions to this work, especially to Jim Lee, Deborah Fein, George Niemann, Judy Dwyer, Ann Aldershof and Pablo DeVanzo for criticism and encouragement at many points. Support from the Charles and Sara Goldberg Charitable Trust and a grant from the March of Dimes are gratefully acknowledged.

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SUMMARY
The authors obtained neurological assessments and psychiatric family history data for 40 children with autistic spectrum disorders (autism, Asperger syndrome and pervasive developmental disorder). Neurological evaluation included EEG, MRI, karyotyping and positron emission tomography as indicated. Family history data were obtained from family members during long-term follow-up. 20 probands had positive neurological findings, 18 with negative family history. 14 had no neurological findings and positive family histories; they tended to have higher function. Six had neither, and two had both. The segregation of neurological findings and familial affective disorder was highly significant. These findings suggest that an important subgroup of autistic spectrum disorders may be related etiologically to familial major affective disorders, and may represent the early-life onset of a severe phenotype of major affective, particularly bipolar, disease.

RÉSUMÉ
Histoires familiales psychiatriques et affections neurologiques dans les affections regroupées dans l'autisme
Les auteurs ont obtenu des donneés d'évaluation neurologique et d'histoire familiale psychiatrique pour 40 enfants présentant des affections de type autistique (autisme, syndrome d'Asperger et troubles développementaux envahissants). L'évaluation neurologique incluait l'EEG. l'IRM, le caryotype et une tomographie à émission de positrons chaque fois que cela était indiqué. Les données d'histoires familiales étaient obtenues des membres de la famille durant un suivi à long terme. Des données neurologiques positives ont été retrouvées dans 20 cas, pas de histoire psychiatrique familiale dans 18 cas. Dans 14 cas, il n'y avait pas de données neurologiques, mais une histoire familiale psychiatrique; ces enfants semblaient moins atteints. Six cas ne présentaient ni données neurologiques ni histoire psychiatrique alors que dans deux cas, il y avait à la fois données neurologiques et histoire psychiatrique. L'occurence élevée de données neurologiques ou d'histoire familiale psychiatrique était hautement significative. Ces données suggèrent qu'un sousgroupe important d'affections rattachées au spectre de l'autisme peut être relié sur le plan étiologique à des troubles affectifs familiaux majeurs et peut traduire une début précoce d'un phénotype grave d'une affection affective majeure, notamment bipolaire.

ZUSAMMENFASSUNG
Psychiatrische Familienanamnese und neurologische Erkrankungen bei autistischen Störungen
Die Autoren haben 40 Kinder mit autistischen Störungen (Autismus, Asperger Syndrom und pervasive Entwicklungsstörungen) neurologisch untersucht und Daten über die psychiatrische Familienanamnese erhoben. Die neurologische Untersuchung beinhaltete EEG, MRI, Chromosomenanalyse un Positronen-Emissionstomographie. Die Daten für die Familienanamnese wurde von Familienmitgliedern im Verlauf der Langzeituntersuchungen erhoben. 20 Probanden hatten positive neurologische Befunde, 18 davon mit negativer Familienanamnese. 14 hatten keine neurologischen Befunde, aber eine positive Familienanamnese; bei ihnen wurden eher bessere Funktionen festgestellt. Sechs hatten weder neurologische Befunde noch eine Familienanamnese und zwei hatten beides. Die Trennung von neurologischen Befunden und familiären Gemütskrankheiten war hochsignifikant. Diese Befunde weisen darauf hin, daß eine wichtige Untergruppe des Spektrums der autistischen Erkrankungen ätiologisch wahrscheinlich zu den familiären Gemütskrankheiten gehört und vielleicht der frühkindliche Beginn einer schweren Form einer Gemütskrankheit ist.

RESUMEN

Historia familiar psiquiátrica y enfermedad neurológica en alteracione de tipo autístico

Los autores consiguieron evaluaciones neurológicas e historia familiar psiquiátrica en 40 niños con alteraciones de tipo autístico (autismo, sindrome de Asperger y alteración pervasiva del desarrollo). La evaluación neurológica incluyó EEG, IRM, cariotipo y tomografía por emisión de positrones, segun los casos. Los datos de la historia familiar se obtuvieron a partir de familiares durante un largo tiempo de seguimiento. 20 de los probandos tenían hallazgos neurológicos positivos y de ellos en 18 había una historia familiar negativa; 14 no tenían hallazgos neurológicos y sí historias familiares positivas; tendían a tener una función mayor. Siete no tenían ni hallazgos neurológicos ni historia familiar y dos casos tenían ambas cosas. La segregación de los datos neurológicos y la afección afectiva familiar era altamente significativa. Estos hallazgos sugieren fue un importante subgrupo de alteraciones autísticas pue de tener una relación etiológica con alteraciones familiares afectivas mayores y pueden representar el inicio en edad precoz de un grave fenotipo de alteración afectiva mayor, especialmente bipolar.

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