

INTERNATIONAL CONSENSUS STATEMENT
ON ADHD

To the Editor:

I am writing in hopes of alerting your extensive readership to the recent publication of the International Consensus Statement on attention-deficit/hyperactivity disorder (ADHD) that recently appeared in *Clinical Child and Family Psychology Review* (June 2002), and which can be accessed through their Web site (www.kluweronline.com/issn/1096-4037; then click on journal contents, then June 2002 issue, then International Consensus Statement). It is also available through the Web site for Children and Adults with ADHD (chadd.org). The document has been translated into several foreign languages, is being distributed internationally through efforts of the many signers and other advocates for ADHD, and has been given to numerous journalists who have contacted the signers for information on ADHD. We encourage your readers to do the same.

This statement, signed by more than 80 of the world's leading clinical researchers investigating ADHD and related childhood disorders, and providing hundreds of supporting references, is a milestone in child mental disorders. Never before have so many international experts joined together in an independently initiated campaign to correct the rampant misinformation frequently appearing in the world media concerning a childhood mental disorder, its nature, causes, and management, especially via medication. Yet so frustrated have the signers, and others, become of the manner in which today's journalists oversimplify, mislead, and sensationalize their coverage of this disorder that this document became essential to develop and disseminate.

Please let your readers know of the availability of this consensus statement, and thank you for your own input and assistance with its creation.

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ADOPTION STUDY OF ADHD

To the Editor:

In 2000, Sprich and colleagues published the results of an attention-deficit hyperactivity disorder (ADHD) adoption

study in this *Journal*. The investigators identified an adoptive hyperactive (AH) group of 25 adopted children with ADHD and their 62 first-degree adoptive relatives, a biological hyperactive (BH) group of 101 children with ADHD and their 310 biological relatives, and a biological normal (BN) group of 50 non-ADHD children and their 153 first-degree biological relatives. The results showed that the BH relative group had a significantly higher ADHD diagnosis rate versus the AH and BN relatives. The investigators concluded that their results "add to mounting evidence from multiple lines of research strongly supporting the genetic hypothesis for ADHD" (p. 1436).

Sprich and colleagues' study, however, used the "adoptive family" method, whose methodological limitations have been discussed in detail elsewhere (Joseph, 2000a,b). There are two main problems with the adoptive family method. (1) In most cases, adoptive parents are screened for mental health problems as part of the adoption process. Thus it is not surprising that "rates of disorder and cognitive and psychological dysfunction were quite low" among the AH adoptive parents (Sprich et al., 2000, p. 1436). (2) In contrast to the *schizophrenia* adoption studies carried out in Denmark, Finland, and the United States, researchers using the adoptive family design do not study the biological and adoptive relatives of the *same* adoptee. These problems raise doubts about the validity of concluding in favor of genetic influences on ADHD from the Sprich et al. data. On the positive side, this was the first-ever ADHD adoption study to make diagnoses blindly.

Still another problem was Sprich and colleagues' failure to establish an adoptive normal group of adopted non-ADHD children: "It would have been interesting to include a group of adopted non-ADHD probands [i.e., children] for comparison" (p. 1436). Although the investigators viewed this omission as only a minor flaw, in the 1999 Faraone et al. psychiatric genetics textbook an adoptee control group was seen as a *requirement* for psychiatric adoption studies. According to Faraone and colleagues, "The increased risk for psychiatric disorders among adoptees limits generalizability and *demands* that any psychiatric study of adoptees use an adoptee control group" (Faraone et al., 1999, p. 42, emphasis added). Thus, by this one standard set by leading psychiatric geneticists (one of whom was Sprich's collaborator), the study is methodologically unsound. Yet another problem is that adoptees were placed into their adoptive homes as late as 1 year after birth and that "only a minority of available subjects had been adopted at birth or shortly thereafter *as we required for inclusion in this study*" (Sprich et al., 2000, p. 1436, emphasis added). If only a minority of adoptees met the

investigators' stated requirements, it would seem that they were unable to control for the confounding features introduced by late placement. Again, this change of criteria limits genetic inferences on the basis of Faraone and colleagues' description: "If a child has lived with a parent for even a short period of time prior to adoption, the biological relationship will have been 'contaminated' by the environment created the child's biologic parents" (Faraone et al., 1999, p. 43).

Finally, although Sprich and colleagues had written earlier (p. 1432) that the "etiology [of ADHD] remains unknown," they advised clinicians working with adoptive parents of children with ADHD to "emphasize that environmental factors were not likely the cause of the adoptive child's problems" (p. 1436). But even if genetic factors were important, their advice is potentially misleading. Almost everyone in the field can agree that environmental factors play at least some role in the etiology of ADHD-type behavior. Thus the discovery and elimination of a particular environmental trigger could effectively eliminate this type of behavior, regardless of the "strength" of a child's genetic predisposition. Would Sprich and colleagues inform parents of neonates genetically susceptible to phenylketonuria that environmental factors do not cause the disorder?

To summarize, apart from having made blind diagnoses, the Sprich et al. (2000) study is susceptible to the invalidating methodological problems of the earlier ADHD adoptive family studies and violated standards established by leading psychiatric geneticists near the time the study was published. Because twin studies are subject to even more methodological problems and environmental confounds than adoption studies (Joseph, 2000a, 2002), it is important that clinicians and researchers evaluate the evidence from twin and adoption studies with a critical eye.

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Faraone SV, Tsuang MT, Tsuang DW (1999), *Genetics of Mental Disorders*. New York: Guilford

Joseph J (2000a), Not in their genes: a critical view of the genetics of attention-deficit hyperactivity disorder. *Dev Rev* 20:539-567

Joseph J (2000b), Problems in psychiatric genetic research: a reply to Faraone and Biederman. *Dev Rev* 20:582-593

Joseph J (2002), *The Gene Illusion: Genetic Research in Psychiatry and Psychology Under the Microscope*. Ross-on-Wye, UK: PCCS Books

Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV (2000), Adoptive and biological families of children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry* 39:1432-1437

DOI: 10.1097/01.CHI.0000024883.60748.E3

Drs. Biederman and Faraone reply:

Joseph's letter about our adoption study of ADHD (Sprich et al., 2000) provides a useful opportunity to clarify misconceptions about methods in genetic epidemiology and the implications of genetic data for clinical practice. He correctly urges caution

in the interpretation of our study given the limitations of our methodology. But that is not news. We described our study's limitations in the original article and, as our other work indicates, are well aware of methodological issues in genetic epidemiology (Faraone et al., 1999).

We disagree that our adoption study's limitations invalidate its main conclusion, viz., that it adds to mounting evidence from multiple lines of research supporting the idea that genes influence susceptibility to ADHD. As we describe in more detail elsewhere (Faraone and Biederman, 2000), Joseph's critiques of genetic studies do not attend to the nature of scientific theory building and hypothesis testing.

The theory that genes influence ADHD is a viable theory because it makes several testable predictions: (1) ADHD should run in families. It does (Faraone and Doyle, 2001). (2) Identical twins should show a greater concordance for ADHD than fraternal twins. They do (Faraone and Doyle, 2001). (3) ADHD should be transmitted through biological, not adoptive family relationships. It is (Faraone and Doyle, 2001). (4) The familial transmission of ADHD should conform to genetic, not cultural transmission, models. It does (Faraone and Doyle, 2001). (5) Molecular genetic studies should find evidence that specific genes cause ADHD. They have (Faraone and Doyle, 2001).

In our view, the theory that genes influence ADHD has not been disproved. Our choice of language corresponds to the logic of scientific inference. Experiments subject theories to falsification. They can fail to falsify a theory but cannot prove that it is correct. For genetic studies of ADHD, the consistent failures to falsify the genetic influence theory strengthen our belief that the theory is true.

We should also address the principle of parsimony when considering the value of alternative theories. Put simply, other things being equal, a theory that makes fewer assumptions is preferable to one requiring more assumptions. Any genetic theory of ADHD explains the family, twin, adoption, and molecular genetic data with one idea, the idea that genes influence the etiology of ADHD. In contrast, the theory that genes do not influence ADHD requires a fairly complex theory, with many nongenetic mechanisms, to explain the pattern of data. One nongenetic mechanism must explain transmission from parent to child. Another nongenetic mechanism must be invoked to account for twin data. A third nongenetic mechanism must explain the results of adoption studies, and a fourth must explain findings from molecular genetic studies. It is, of course, possible that four different mechanisms have converged to produce a pattern of results that simulates genetic transmission. But such a theory is not parsimonious, especially when compared with the idea that genes account for the observed data.

Joseph misinterpreted our advice to clinicians to emphasize that environmental factors were not likely the cause of ADHD for adoptive children. This was not meant as a prescription for treatment but as a guideline for the clinician's education for

parents of children with ADHD, who are continually bombarded by media claims that ADHD is caused by weak family structures or poor parenting skills. Such claims fly in the face of genetic epidemiological and neuroimaging data which show ADHD to be a brain disorder strongly influenced by genes (Faraone and Biederman, 1998). These data suggest that, rather than blame parents for creating toxic environments, clinicians should educate them about the brain basis of the disorder as such education can potentially improve treatment adherence.

On the other hand, clinicians should not confuse the etiology of a disorder with its treatment. It is wrong to believe that a genetic cause for a disorder means that psychosocial therapies will be useless. The idea that genes cause a disorder does not rule out the possibility that psychosocial risk factors also influence its etiology or modulate its course.

We appreciate Joseph's criticisms in the spirit of healthy scientific debate. We also hope his ideas will lead to testable hypotheses that will further the growth of scientific literature and clarify the details of how genes and environment cause ADHD and moderate its course.

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Sprich S, Biederman J, Crawford MH, Mundy E, Faraone SV (2000), Adoptive and biological families of children and adolescents with ADHD. *J Am Acad Child Adolesc Psychiatry* 39:1432-1437
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SMOKING AND ALCOHOL USE IN PREGNANCY

To the Editor:

In a recent issue of this *Journal*, Mick et al. reported an increased risk of attention-deficit hyperactivity disorder (ADHD) in the offspring of mothers with a high alcohol intake as well as heavy smokers (Mick et al., 2002). This is the third report from this research group on smoking, but the first on alcohol. The study is of interest given the fact that sound evidence is lacking. The public health relevance is obvious, providing their findings reflect causal mechanisms.

Mick et al. compiled data from two case-control studies to study the association between heavy alcohol drinking in pregnancy and ADHD in the offspring: a study on boys reported in 1996 (Milberger et al., 1996) and a study on girls reported

in 1999 (Biederman et al., 1999). The authors found that 4% (10/280) of the case-mothers drank alcoholic beverages daily compared with 2% (5/242) among controls, which leads to a crude odds ratio of 1.8 (95% confidence interval: 0.6-5.8). The authors present an adjusted odds ratio of only 2.5 (95% confidence interval: 1.1-5.5). What caused this powerful negative confounding? A high alcohol intake normally correlates with other risk factors, and subsequently a correction in the opposite direction would be expected.

The authors state that gender did not modify the associations between ADHD and the exposures studied. The odds ratio between alcohol intake and ADHD was 1.3 in males and 3.6 in females. Although this difference is not statistically significant, absence of evidence of an effect is not evidence for absence of an effect: Their statistical power to detect even an important effect modifier is very low.

The proportion of drinkers in the control group in the female study was lower than in the control group in the male study. This difference was greater than the difference between cases and controls in any of the studies. Changes in alcohol consumption habits during pregnancy in the period between the two studies could be the explanation, as could bias. Nonetheless, the association between alcohol intake in pregnancy and ADHD in the offspring in this study rests entirely upon the low prevalence of drinkers among controls in the female study. Consequently this throws doubt on whether their control group reflects the use of alcohol in the study base (children who would have been cases if they had symptoms, who qualified for the ADHD diagnosis).

The present study almost certainly provides a better estimate of the association between heavy smoking in pregnancy and ADHD in the offspring than the previous reports. The estimate presented by Milberger et al. in 1996 was based on a smaller sample, the same boys as in the present study. Milberger and colleagues' study of 1998 investigated 173 siblings of these 140 boys with ADHD. Siblings with diagnosed ADHD were the cases, and siblings without ADHD served as controls. Among the case-mothers, 47% were heavy smokers compared with 24% in controls. The reported adjusted odds ratio of 4.4 is clearly an overestimation, and again we would anticipate negative confounding of the risk factors they controlled for. Milberger et al. (1998) also permitted some of the women to participate in the analysis with more than one child without adjusting for the dependency this aspect creates.

In this study Milberger et al. broke one of the basic rules of a case-control design. In a study where the cases define the study population, controls still have to provide valid estimates of the exposure distribution in the underlying study population. In no way will siblings fulfill these basic requirements, which in part is due to overmatching, and it is unclear what is actually measured. The authors might have used their data to determine whether ADHD risk in siblings of a given mother depends on her smoking status during that pregnancy. To do

this, they would have had to report differences in smoking habits during the sibling pregnancies.

Finally, as pointed out by Mick et al., these studies are subject to recall bias because they are based on retrospective self-reports and the symmetry in the incentive to report smoking may be impaired for cases and controls. A study based on smoking data recorded during pregnancy is needed to bring these associations to the test. In other words, we await well-performed follow-up studies to clarify the possible association between smoking and alcohol during pregnancy and ADHD in the offspring before we are ready to make any causal inference.

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Biederman J, Faraone SV, Mick E et al. (1999), Clinical correlates of ADHD in females: findings from a large group of girls ascertained from pediatric and psychiatric referral sources. *J Am Acad Child Adolesc Psychiatry* 38:966-975

Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S (2002), Case-control study of attention-deficit hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry* 41:378-385

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Milberger S, Biederman J, Faraone SV, Jones J (1998), Further evidence of an association between maternal smoking during pregnancy and attention deficit hyperactivity disorder: findings from a high-risk sample of siblings. *J Clin Child Psychol* 27:352-358

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Dr. Mick replies:

Obel et al. raise some important questions regarding our recent article examining the risk of ADHD associated with prenatal exposure to cigarettes, alcohol, and other drugs (Mick et al., 2002). I appreciate their comments and interest and welcome the opportunity to clarify the methods used to arrive at our results.

Because these were case-control data, the measure of exposure was particularly susceptible to a recall bias in which mothers of cases and mothers of controls reported exposure history with different levels of accuracy. For these data the true exposure is not known. We assessed exposure from a direct assessment of the mother in which we asked her about her behavior during pregnancy with each of her children. Traditionally, this measure should be most susceptible to recall bias because the mother was aware at the time of interview that we are asking questions about potential exposures.

Because this study was part of an ongoing family study, we also had access to independent self-report interviews of the mother in which we diagnosed the lifetime history, onset, and offset of *DSM-III-R* disorders. Using these onsets and offsets and the age of the child, we created a second, indirectly assessed measure of exposure to alcohol or drug abuse or dependence during pregnancy. We call this indirect because the mother was not aware that the information she was providing regarding her own history would later be used to define measures of prenatal exposure for her children.

The difference between adjusted odds ratios calculated with logistic regression and those that result from the raw numbers of exposed and nonexposed cases and controls was not due to negative confounding, but rather because we incorporated more information than what Obel et al. reference in their communication. We used a new method of incorporating exposure information from more than one source in an attempt to estimate potential recall bias (Horton et al., 1999). Table 1 illustrates all of the odds ratios (ORs) that were used to calculate an overall effect of 2.5.

As shown in Total column of this table, the direct and indirect measures of exposure result in different ORs. Both of these ORs are susceptible to error, and neither is totally accurate. We used bivariate logistic regression to utilize the shared and unique information that each exposure provided.

TABLE 1
 Odds Ratios Used to Calculate Overall Effect of 2.5

	Total ad/bc = OR	Males ad/bc = OR	Females ad/bc = OR
Direct exposure assessment	(10)(237)/(270)(5) = 1.8	(6)(116)/(134)(4) = 1.3	(4)(121)/(136)(1) = 3.5
Indirect exposure assessment	(15)(238)/(265)(4) = 3.4	(6)(119)/(134)(1) = 5.3	(9)(119)/(131)(3) = 2.7

Obel et al. are also concerned that all of the effect reported was carried by the very low prevalence of exposure in female controls. Again, when all of the measures are included we can see that this was not the case.

We did not find that gender modified the ORs reported for prenatal exposure to either alcohol or cigarettes. We mention in the limitations section of the article that this should be viewed with caution because the power to detect such an interaction was low. Furthermore, we highlighted the low frequency in some cells by presenting the prevalence of exposure stratified by gender. We believe that each of these steps appropriately conveys the level of confidence that should be placed on this statistically insignificant interaction.

Regarding the critique of Milberger and colleagues' (1998) analyses of our data, I respectfully disagree with the conclusions made by Obel et al. The single most important factor in selecting controls is that they be representative of the exposure distribution of the population that gave rise to the cases. In the Milberger et al. (1998) study, siblings of cases would certainly fit the bill. The limitation with using controls that are so intimately related with the cases is that there may not be enough variability in exposure to detect a true effect. However, this would lead to an underestimate of the true effect and not, as Obel et al. assert, a clearly inflated estimate.

Using siblings as control subjects also violates the assumption of most statistical tests that each observation is independent of the others. It is not correct that Milberger et al. failed to adjust for this dependency, however, as they used a robust estimator of variance which results in consistent *p* values that are robust to the misspecification of the correlation between related individuals. Nonetheless, violating this assumption would only have impacted estimates of statistical significance and not any of the point estimates made.

At the root of each of these questions and concerns are the inherent limitations of retrospective case-control studies. I must agree with Obel et al. that this research is in need of replication by multiple sources in a variety of settings before any causal association may be asserted.

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Horton N, Laird N, Zahner G (1999), Use of multiple informant data as a predictor in psychiatric epidemiology. *Int J Methods Psychiatr Res* 8:6–18

Mick E, Biederman J, Faraone SV, Sayer J, Kleinman S (2002), Case-control study of attention-deficit/hyperactivity disorder and maternal smoking, alcohol use, and drug use during pregnancy. *J Am Acad Child Adolesc Psychiatry* 41:378–385

Milberger S, Biederman J, Faraone S, Jones J (1998), Further evidence of an association between maternal smoking during pregnancy and attention deficit hyperactivity disorder: findings from a high-risk sample of siblings. *J Clin Child Psychol* 3:352–358

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AUTISTIC SPECTRUM DISORDER?

To the Editor:

Szatmari and colleagues' (2002) remarkable paper shows that the phenotypic variation in infantile autism is not a unitary construct and is composed of at least two distinct dimensions of autistic symptoms and levels of functioning. The authors point out: "The finding that two separate dimensions of severity exist is not compatible with the model that a 'spectrum' of autistic disorders alone will capture meaningful variation in clinical presentation" (p. 474). But at no point do the authors mention that the term *autistic spectrum disorder* (ASD) is not an internationally recognized diagnostic category. This "disorder" is absent from the two main official psychiatric nomenclatures, the *DSM-IV* (American Psychiatric Association, 1994) and the *ICD-10* (World Health Organisation, 1993). The use of the word *disorder* suggests that ASD would be a *DSM* category. Indeed, *mental disorder* replaced in *DSM* the concept of *reaction* and a definition of mental disorder has been included in the manual since the publication of the *DSM-III*. The concept of ASD is considered by some authors (Charman and Baird, 2002) as interchangeable with the term *pervasive developmental disorder* (PDD). PDD is a concept introduced in 1980 in the *DSM-III* as the category covering the subgroups of infantile autism and childhood-onset pervasive developmental disorders. This term has been kept since and the *DSM-IV* states that PDD "are characterized by severe and pervasive impairment in several areas of development: reciprocal social interaction skills, communication skills, or the presence of stereotyped behavior, interests, and activities.... This section [PDD] contains Autistic Disorder, Rett's Disorder, Childhood Disintegrative Disorder, Asperger's Disorder, and Pervasive Developmental Disorder Not Otherwise Specified" (American Psychiatric Association, 1994, p. 65). There is no mention of an ASD in the chapter on PDD.

Internationally recognized psychiatric classifications like the *DSM* are based on thorough and careful testing of new hypotheses through painstaking epidemiological studies. Authors cannot decide to include in it their preferred theories before these new theories have been proven right. However, in view of the findings of Szatmari and his colleagues, the concept of autistic spectrum does not seem a very likely candidate for inclusion in a future version of the *DSM*.

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American Psychiatric Association (1994), *Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV)*. Washington, DC: American Psychiatric Association

Charman C, Baird G (2002), Practitioner review: diagnosis of autistic spectrum disorder in 2- and 3-year-old children. *J Child Psychol Psychiatry* 43:289–305

Szatmari P, Merette C, Bryson S et al. (2002), Quantifying dimensions in autism: a factor-analytic study. *J Am Acad Child Adolesc Psychiatry* 41:467–474
 World Health Organisation (1993), *Mental Disorders: A Glossary and Guide to Their Classification in Accordance With the 10th Revision of the International Classification of Diseases: Research Diagnostic Criteria*. Geneva: World Health Organisation
 DOI: 10.1097/01.CHI.0000024887.60748.F6

Dr. Szatmari et al. reply:

Dr. Bailly makes a good point in his thoughtful letter, and we appreciate the opportunity to respond. The term *autistic spectrum disorder* (ASD) is not part of either official classification system. The question is whether it *should* be and so replace the term *pervasive developmental disorder* (PDD) as a way of understanding children who present with developmental impairments in social reciprocity, communication, and play. It is our impression, at least in North America, that many professionals and parents prefer the term ASD because, to them, it describes more accurately than the term PDD the relationship between autism, Asperger's disorder, and PDD-not otherwise specified (NOS). These two labels suggest a subtle but quite different understanding of the clinical variation seen in children with these diagnoses. The term PDD implies that the distinctions between the subtypes (autism, Asperger, and PDD-NOS) are meaningful; the term ASD implies that the distinctions are more arbitrary than real and that the clinical variation observed is better captured by the notion of a single spectrum. Perhaps no other issue in our paper generated as much good-natured debate with the *Journal's* perceptive reviewers than the very sentence quoted by Dr. Bailly! Our finding that autistic symptoms and level of functioning represent independent latent constructs is incompatible with the notion of a *single* spectrum of clinical variation. But then again the evidence that the term PDD is a more accurate reflection of the state of affairs is little better.

The more fundamental problem is of course the poverty of our language. We try to use a static category like "disorder" to describe a developmental process. It is worse than forcing a square peg into a round hole; it is more like forcing a powerful moving object to stand still. These are *developmental* disabilities and their relationship needs to be understood in a developmental context, not a cross-sectional one (which is what *DSM* and *ICD* are based on).

Dr. Bailly believes that "psychiatric classifications like the *DSM* are based on thorough and careful testing of new hypotheses through painstaking epidemiological studies." Alas, would that it were so! The adoption of diagnostic labels is also a matter of public policy, and the relationship between evidence and policy is often tenuous, if not sometimes completely discontinuous. This is not to say that the specification of reliable diagnostic criteria has not been a good thing. There is little question that this is perhaps the major achievement of academic psy-

chiatry in the last century. "Some achievement!" you may say, but nevertheless it is true. The lesson is that we should not reify a useful but as yet incomplete and imperfect conceptualization. Sometimes, the goal of clinical investigation is not to discover the truth, but to learn the error of our ways. In the meantime, it is better not to know than to know the wrong thing.

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GENDER-NONCONFORMING BOYS

To the Editor:

I am writing in response to the excellent article titled "A Support Group for Parents of Gender-Nonconforming Boys," published in the August issue of the *Journal* (Menvielle and Tuerk, 2002). The authors state, "Half of the target children were adopted. Overrepresentation of adoptees is commonly observed in this clinical population...."

There were no adopted children in my sample of 28 children with gender identity issues, described in my Clinical Perspectives article in the May issue of the *Journal* (Rosenberg, 2002). Since my article was written, I have seen four additional children with gender identity issues, none of whom was adopted. This illustrates the difficulties of drawing conclusions from clinical studies of uncommon conditions, yielding small sample sizes.

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 Rosenberg M (2002), Children with gender identity issues and their parents in individual and group treatment. *J Am Acad Child Adolesc Psychiatry* 41:619–621
 DOI: 10.1097/01.CHI.0000024888.60748.12

FOLLOW-UP OF A CASE OF MUNCHAUSEN BY PROXY SYNDROME

To the Editor:

A Grand Rounds published in this *Journal* (Sugar et al., 1991) described "Billy," a 3-year-old child, who was separated from his mother because she was suspected of causing his chronic diarrhea after the hospital found phenolphthalein in his stool. During this separation period and while in the hospital, Billy "became so spiritless, withdrawn and passive that he...needed to be carried." His electrolyte levels and other physiological parameters were normal, so "one of the doctors took him on a [weekend] family outing," but to little avail. The mother was concerned and planned to return to the hospital the next day, but that night the resident was called to see Billy because he appeared very listless, and while they were talking, "[he] stopped breathing and could not be revived." "An autopsy was reported as entirely normal, as were toxic screens." Child Protective Services closed the case.

In 1996, one of the authors of this letter (H.S.) was consulting at another hospital in the same city and had a case presented that involved a child referred by a pediatrician because of cachexia and diarrhea. This 12-year-old child had developed a seizure disorder at age 1 year, around the time of his brother's unexplained death. From the history the staff recognized that this patient was Billy's younger brother. They considered a diagnosis of Munchausen by proxy syndrome (MBP), but were harangued by the child's pediatrician. A hospital consultant felt that this was not MBP and that such a formulation would only be hurtful to the diagnostic and therapeutic process. Furthermore, after discharge two consulting psychiatrists ruled out MBP, one having described being "deeply impressed with the mother-child interaction."

Years later this case was mentioned at a presentation by H.S. at a child abuse conference. The other author (L.R.R.) recognized the case and reported that "Lee" (the name given to the sibling of "Billy") was admitted at age 14 to a hospital in a different state for deteriorating neurological status from presumed mitochondrial encephalopathy lactic acidosis and stroke-like syndrome (MELAS). Because some elements of his presentation suggested narcotic and/or benzodiazepine poisoning (palliative medications that had been discontinued weeks earlier) and because all tests for MELAS were negative, an astute intensivist sent a urine sample for a toxicology screen. It was positive for benzodiazepines, opiates, and salicylates. Chronic salicylate poisoning perfectly explained Lee's clinical deterioration over the preceding several months.

Within days, Lee, who had been bed-bound, who had not been fed anything by mouth for months, and who was receiving end-of-life care for MELAS, began ambulating and eating normally. Two years later he continues to be completely physically

healthy. He is receiving mental health services and wishes to reunite with his mother when he is out of state custody at age 18.

From these cases we conclude the following:

1. A purely psychological evaluation of a mother and child should not be used to rule out MBP. Only those experienced with the disorder and who can also review or get help with the medical aspects of the case should be involved in these cases. MBP first requires that abuse be demonstrated, through pediatric condition falsification. Next, attempts to understand the mother's motivation, usually discernible from the way the case unfolded over time, need to be made. Self-serving psychological needs is the requirement for factitious disorder by proxy, which is the appropriate diagnosis in the mother. (Ayoub et al., 2002) The child may have bone fide illness as well, and other motivations, e.g., monetary gain, can coexist, but the psychological motivation of attention seeking and need to manipulate powerful medical and nonmedical personnel must be seen as paramount.
2. A forensic or postmortem evaluation is only as good as it is thorough. The toxicology screen in Billy's case appears only to have included arsenic.
3. The cunning of the mothers in producing hard-to-figure-out illnesses is often matched by professionals' disbelief that such a "loving" and attentive mother could possibly be harming her child in this fashion. Few of us by training or nature are able to extract ourselves from the manipulations of those capable of pretending to be good mothers (Schreier and Libow, 1993). It has been recommended that consultants with expertise in MBP, not directly involved, be brought in to review the material.
4. The separation test is also not foolproof, as Billy's case demonstrates.
5. Although the MBP mother has been described as pursuing her abuse compulsively, this has led to a misrepresentation that there can be no hiatus in her activities. Billy did reasonably well until he had to have surgery.
6. Finally, in cases involving MSBP from early in life, the child is unaware of the hand of the mother and frequently the close relationship is something he longs for. Workers in the field have strongly recommended that the abuse by the mother be the focus of the therapy and that there be a telling of the facts jointly or by the professional if the child is unaware.

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LOFEXIDINE IN HYPERACTIVE AND IMPULSIVE CHILDREN WITH AUTISTIC DISORDER

To the Editor:

Autistic disorder is a chronic pervasive developmental disorder, characterized by qualitative impairments in reciprocal social interaction, verbal communication, and nonverbal communication. Good efficacy of clonidine (Jaselskis et al., 1992) as well as of methylphenidate (Birmaher et al., 1988) and neuroleptics is reported. Lofexidine, an α_2 -adrenergic receptor partial agonist similar to clonidine, is most commonly used as a drug withdrawal medication (White et al., 2001).

For this double-blind and placebo-controlled crossover study, 12 outpatient male children who met *ICD-10* criteria for autistic disorder were recruited from the community and clinic. Mean (\pm SD) age was 7.3 ± 2.3 years for lofexidine and 9.2 ± 3.9 years for placebo. Full Scale IQs were obtained with the WISC-R (59 ± 16 for lofexidine and 48 ± 17 for placebo). Agreement of the independent diagnosis of autistic disorder including hyperactivity, distractibility, and impulsivity by at least two child and adolescent psychiatrists was obtained. Parents of all subjects provided written informed consent.

The subjects had no history of identified medical or neurological illnesses and had been off medications for at least 1 month before the study. They lived at home with either both parents (nine subjects) or their mothers (three subjects). Socioeconomic status for the subjects' families was also checked.

All raters (parents, teachers, and clinicians) were blind to drug order until ratings were completed. Lofexidine and identical placebo tablets were administered in a 0.4-mg strength. Tablets for each subject were placed in sealed envelopes designated for each day of the study. Lofexidine or placebo was tapered up over a period of 2 weeks to a dose of 0.8-1.2 mg/day in three doses per day.

Parent-rated instruments included weekly ratings of the 10-item Conners Abbreviated Parent-Teacher Questionnaire (Goyette et al., 1978). Side effects such as increased thirst, drowsiness, sleep disturbance, sadness, dizziness, irritability, appetite change, and decreased activity were also monitored. Weekly teacher ratings included the Aberrant Behavior Checklist (ABC) and the Symptom Checklist (Aman et al., 1985).

A 15-minute videotape paradigm was constructed to determine clinician ratings of the effects of lofexidine on hyperactivity, impulsiveness, and attention. Clinician ratings (average of both raters) consisted of videotaped observations at baseline, 6 weeks, and 13 weeks.

Blood pressure and clinical symptoms were monitored via telephone conversations and scheduled visits. School nurses or the family physician measured blood pressure on a weekly basis. Dosage was blindly titrated downward for significant side effects.

Doses were blindly tapered during week 7 and subjects crossed over to placebo or lofexidine at the beginning of week 8, which was continued during weeks 8 through 13. Parent and teacher ratings were averaged over each 6-week treatment period. Clinician ratings were made only at the end of each treatment period. Ratings during placebo and drug treatment were compared by using paired, two-tailed *t* tests. Statistics were computed with SPSS V9.0. Because there was not a significant effect of the order of drug administration on ratings, the lofexidine and placebo treatment phases were considered together for both treatment groups.

Mean weekly parent ratings on the Conners Parent-Teacher Questionnaire as well as teacher's ratings on the various ABC factors and the symptom checklist scores revealed a significant improvement on lofexidine (Table 1). None of the clinician ratings showed significant differences between lofexidine and placebo. Three patients required blinded downward adjustment of medication because of hypotension.

This double-blind, placebo-controlled study showed a modest improvement mainly of hyperactivity, and the children taking lofexidine showed no sedation. The treatment effect of greatest size was a decrease in the ABC hyperactivity factor.

Very few specific clinical instruments target the response of hyperactive behavior to drug treatment in autistic persons. Both parents and teachers remarked that several of the items on the questionnaires were irrelevant for evaluating their autistic child.

The environment in which clinician ratings were performed was not optimal to serve as a sensitive indicator of the modest effects of lofexidine during the 6-week trial. In addition, this study involved only a small number of subjects.

Assessment of central noradrenergic function through the study of growth hormone release would be helpful in any future studies of possible tolerance to lofexidine. Controlled, long-

TABLE 1
 Comparison of Lofexidine and Placebo
 (Mean, Standard Deviation, *t* Test Values)

	Lofexidine	Placebo	<i>t</i>	<i>p</i>
Conner scale	8.4 \pm 5.1	9.7 \pm 4.8	1.12	.02
ABC				
Irritability	11.4 \pm 7.5	15.7 \pm 8.3	1.35	.03
Hyperactivity	22.7 \pm 12.4	27.8 \pm 11.3	1.24	.01
Stereotypy	6.8 \pm 5.9	8.5 \pm 6.2	1.11	.04
Inap. Speech	6.0 \pm 3.8	5.2 \pm 2.7	1.37	.03
Symptom Checklist				
Drowsiness	3.9 \pm 3.5	0.9 \pm 0.8	1.06	.02
Decr. Activity	4.3 \pm 3.0	2.8 \pm 2.5	1.36	.02

term pharmacological trials with clinical observations in the school and home settings will be necessary to delineate further the role of lofexidine in treating this specific population.

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