CORRESPONDENCE

Retraction: Shamim et al. Nonsurgical Reduction of the Interventricular Septum in Patients with Hypertrophic Cardiomyopathy. N Engl J Med 2002;347:1326-33.

TO THE EDITOR: On October 24, 2002, an article about septal ablation with alcohol for hypertrophic cardiomyopathy was published in the *Journal*.[1] The majority of those named as authors of the article did not have an opportunity to review and verify the data and to approve the manuscript. This unfortunate situation came to light when the article was published. In view of this irregularity in the submission process, we request that that paper be retracted. We believe that the alcohol-ablation technique described is a useful procedure in selected patients with hypertrophic cardiomyopathy, and other data support this view.[2,3] We also want to make clear that the Cleveland Clinic Foundation was not involved in the study but was mentioned purely as an address for correspondence. We hope that readers of the *Journal* will understand that this retraction is designed to maintain the integrity of the scientific process.

Andrew J.S. Coats, M.D.
Michael Henein, Ph.D.
Marcus Flather, F.R.C.P.
Ulrich Sigwart, M.D.
Hubert Seggewiss, M.D.
Duolao Wang, Ph.D.
Mohammed Yousufuddin, M.D.
Waqar Shamim, M.D.

1. Shamim W, Yousufuddin M, Wang D, et al. Nonsurgical reduction of the interventricular septum in patients with hypertrophic cardiomyopathy. N Engl J Med 2002;347:1326-33.
2. Faber L, Meissner A, Ziemessen P, Seggewiss H. Percutaneous transluminal septal myocardial ablation for hypertrophic obstructive cardiomyopathy: long term follow up of the first series of 25 patients. Heart 2000;83:326-31.
3. Mazur W, Nagueh SF, Lakkis NM, et al. Regression of left ventricular hypertrophy after nonsurgical septal reduction therapy for hypertrophic obstructive cardiomyopathy. Circulation 2001;103:1492-6.

Measles, Mumps, and Rubella Vaccination and Autism

TO THE EDITOR: The publication of a controlled epidemiologic study on the measles, mumps, and rubella (MMR) vaccine and autism (Nov. 7 issue)[1] represents a major advance. The great volume of material circulating on the Internet about a possible link between the MMR vaccine and autism cannot undermine the strength of the design. However, the study has some methodologic problems. A review of the clinical records for only 40 of the 316 children with autistic disorder is inadequate. That was clear in another review, which focused on 493 self-selected British children with autistic syndrome[2]: without a multidisciplinary review of lifetime records, important errors would have been unavoidable. Although it would be difficult, with the use of clinical criteria one could identify subgroups among most of the children, notably subgroups with regression.

The power of the current study[1] was high (80 percent to detect a relative risk of 1.5) but misleading. Let us assume hypothetically that there is a vulnerability to MMR-induced disease in 10 percent of the children with autism. We can assume further that 80 percent of the overall group with autism and 95 percent of the subgroup with vulnerability have been vaccinated. In a nested, case–control design within the Danish cohorts, the odds ratio for MMR in the subgroup would be 4.17; for all the children with autism combined, the odds ratio would be 0.97,

masking the association in a small subgroup. Yet, in a conservative estimate, 10 percent would represent 50,000 children in the United States, at a yearly burden of $1.25 billion. I hope this possibility can be ruled out.

Walter O. Spitzer, M.D., M.P.H.

McGill University
Montreal, QC H3G 1A4, Canada

1. Madsen KM, Hviid A, Vestergaard M, et al. A population-based study of measles, mumps, and rubella vaccination and autism. N Engl J Med 2002;347:1477-82.
2. Spitzer WO, Aitken KJ, Dell'Aniello S, Davis MWL. The natural history of autistic syndrome in British children exposed to MMR. Adverse Drug React Toxicol Rev 2001;20:160-3.

TO THE EDITOR: The admirable attempt by Madsen et al. to evaluate a possible association between the MMR vaccine and autism has multiple flaws that compound the bias toward a finding of no association. First, the use of person-years instead of persons in the analysis magnifies the weight of the early cases (when the prevalence of autism was relatively low) and minimizes the weight of the later cases (when the prevalence was five times that in the early period). Second, the mean ages at diagnosis were 51 months for autism and 63 months for other autistic-spectrum disorders. A child born early in the study period had a higher likelihood of receiving a diagnosis than a child born later in the study period. Finally, children in the unvaccinated group underwent a mean of 5.0 years of follow-up (482,360 person-years for 96,648 persons), as compared with 3.7 years in the vaccinated group (1,647,504 person-years for 440,655 persons). This discrepancy also reduced the likelihood that autism would be detected in a vaccinated child as compared with an unvaccinated child.

The authors overstate their conclusion in the abstract by saying, "This study provides strong evidence against the hypothesis that MMR vaccination causes autism." Even if the study did not suffer from these flaws, the strongest defensible conclusion would be that the study did not detect an association between MMR and autism.

Michael E. Mullins, M.D.

Washington University School of Medicine
St. Louis, MO 63110
mullinsm@msnotes.wustl.edu

TO THE EDITOR: Inadequate epidemiologic studies, in contrast with laboratory studies,[1,2] have not found an association between MMR vaccination and autism. Madsen et al. fail to disaggregate the relevant subgroup from the overall population with autism.

My own hypothesis, untested at the population level, involves a subgroup of children with regressive autism associated with gastrointestinal inflammation and apparently type 2 helper T cell (Th2)–skewed mucosal and systemic immunity. In 1999 a colleague and I wrote, "The newborn tends towards a Th2 response to pathogens and gradually shifts towards a Th1 [type 1 helper T cell] response with age. If this transition does not take place appropriately, the infant is likely to be at greater risk of mounting aberrant immune responses in later life."[3] In considering children at risk, cofactors that may interfere with a Th2-to-Th1 transition in infants require examination. Mercury exposure alters the susceptibility to infection. Murine susceptibility to infection with *Leishmania major* reflects a genetically restricted Th2 response. In resistant animals (with a Th1 response to *L. major*), a Th2-mediated autoimmune syndrome develops, and the animals are unable to clear the infection after exposure to mercury.[4]

Hypothesis testing at the population level must adjust for cofactors that might influence the response to MMR — an impossible task, perhaps, given infants' increasing exposure to mercury in vaccines. Answers may be found only in detailed examination of each child.

Andrew J. Wakefield, F.R.C.S., F.R.C.Path.

International Child Development Resource Center
Boca Raton, FL 33431

Editor's note: Dr. Wakefield acts as an expert to the United Kingdom courts in the current MMR class-action suit.

1. Uhlmann V, Martin CM, Sheils O, et al. Potential viral pathogenic mechanism for new variant inflammatory bowel disease. Mol Pathol 2002;55:84-90.
2. Wakefield AJ. Enterocolitis, autism and measles virus. Mol Psychiatry 2002;7:Suppl 2:S44-S46.
3. Wakefield AJ, Montgomery SM. Autism, viral infection and measles-mumps-rubella vaccination. Israeli Med Assoc J 1999;1:183-7.
4. Bagenstose LM, Mentink-Kane MM, Brittingham A, Mosser DM, Monestier M. Mercury enhances susceptibility to murine leishmaniasis. Parasite Immunol 2001;23:633-40.

TO THE EDITOR: Suspicions about vaccine safety, discussed by Campion in his Perspective,[1] are contributing to a growing measles crisis in Japan. In 1995, the government enacted a law making immunizations optional. Because of parents' fear of rare

vaccine-related encephalopathic complications, mounting medicolegal concern on the part of physicians, and limited intervention by the government, compliance with measles vaccination is poor. Cases of measles in Japan now number more than 100,000 per year,[2] with an estimated 50 to 100 deaths annually. The effects of this problem are crossing borders. Of the 86 total cases of measles in the United States in 2000, 62 percent were importation-associated. Twenty-six of the 86 cases (30 percent) were imported. Japan contributed the largest number of cases from a single country (7 of the 26 imported cases).[3]

Measles has the potential to cause substantial morbidity and mortality, not only in the developing world but also in the developed world. Public health authorities have an important role in objectively educating both physicians and the public about vaccines, in supporting physicians in vaccinating children, and in improving vaccination programs. A coordinated global effort will be critical for preventing the spread of vaccine-preventable diseases such as measles.

Katherine K. Noble, M.D.
Katsuyuki Miyasaka, M.D., Ph.D.

National Children's Medical Center
Tokyo 157-8535, Japan
miyasaka-k@ncchd.go.jp

1. Campion EW. Suspicions about the safety of vaccines. N Engl J Med 2002;347:1474-5.
2. Terada K, Niizuma T, Ogita S, Kataoka N. Alterations in epidemics and vaccination for measles during a 20 year period and a strategy for elimination in Kurashiki City, Japan. Kansenshogaku Zasshi 2002;76:180-4. (In Japanese.)
3. Measles — United States, 2000. MMWR Morb Mortal Wkly Rep 2002;51:120-3.

DR. MADSEN REPLIES: Whether it is possible to perform hypothesis testing at all at any level is a matter for debate elsewhere. A hypothesis can, however, be subject to critical evaluation in population-based studies, such as ours. We found no corroboration for the hypothesis that MMR vaccination causes autism.

Dr. Wakefield argues that we should have controlled for mercury exposure from vaccines. However, mercury — or more precisely, the vaccine preservative thimerosal that contains ethyl mercury — has not been used in Danish vaccines since 1992 and thus was not a confounder in the study.

Dr. Spitzer will probably agree that our task is to examine (not to prove) proposed causal links between exposure and diseases. We cannot rule out the possibility that at least one child would not have become autistic if he or she had not been vaccinated, and that point alone may be sufficient for stating causality. Unfortunately, we cannot subject this assumption to a critical test unless it is better specified. We can say that if this causal link exists, it is not frequent. We can say that MMR vaccination is not the explanation for an increasing incidence in autism, if such an increasing incidence exists. We can say that MMR vaccination is not one of the common causes of autism. But we cannot prove anything, especially not when it comes to null hypotheses.

All effect measures have a set of confidence limits that vary in width and credibility according to the size and quality of the study. We do not claim to have proven that MMR vaccination can never cause autism. We can state only that we find nothing in our data to support the hypothesis that MMR causes autism. We cannot rule out the existence of a susceptible subgroup with an increased risk of autism if vaccinated, but such a subgroup must be small. Even if such a hypothetical subgroup exists, its members may be better off receiving the vaccine, when all the risks and benefits are taken into consideration.

We are in the process of evaluating diagnoses for all the cases of autism in the cohort, and so far, the estimates of validity have not changed. This was to be expected, since only specialists in child and adolescent psychiatry were authorized to diagnose autism.

With regard to Dr. Mullins's comments: it is important to note that we did adjust for both age and calendar period in the analysis. Vaccination was treated as a time-dependent covariate, and the vaccinated children contributed risk time in the unvaccinated group until they were vaccinated. Thus, calculating the mean years of follow-up the way Dr. Mullins suggests is not possible.

Kreesten Meldgaard Madsen, M.D.

Danish Epidemiology Science Center
DK-8000 Aarhus C, Denmark
kmm@dadlnet.dk

DR. CAMPION REPLIES: The experience that Drs. Noble and Miyasaka describe is sobering. People want more independence and more control over all health care decisions. However, if the rate of childhood vaccination declines substantially, the result will be needless harm to young children. It is particularly

sad when fears about vaccination begin to spread because of statements in the scientific literature that are hypothetical and unproven. The large, careful study by Madsen et al. found absolutely no evidence to support the hypothesis that MMR vaccination is responsible for the development of autism.

Edward W. Campion, M.D.

Dexamethasone in Adults with Bacterial Meningitis

TO THE EDITOR: The study by de Gans and van de Beek and their colleagues (Nov. 14 issue)[1] demonstrates the benefits of dexamethasone in adults with bacterial meningitis. The authors conclude by recommending dexamethasone for all adults with acute bacterial meningitis. How to operationalize this recommendation poses a problem. In addition to having suspected meningitis, patients in this study had to have cloudy cerebrospinal fluid, bacteria on Gram's staining, or a cerebrospinal fluid white-cell count of more than 1000. Thus, these patients were very likely to have acute bacterial meningitis. Most patients seeking medical attention with suspected meningitis, however, are unlikely to have a bacterial cause, and they typically receive empirical therapy pending complete evaluation. Is it clinically justifiable to wait for the confirmatory data before administering an antibiotic when waiting may constitute a delay in therapy? To avoid this pitfall, the clinical threshold for administering antibiotics is likely to be set much lower than that used in this study.

It is likely that the majority of potential candidates for dexamethasone will not have bacterial meningitis. As the target group becomes diluted by patients without bacterial meningitis, the benefit from dexamethasone will be correspondingly reduced, and the frequency of adverse outcomes may increase. Before recommending the routine use of adjunctive dexamethasone therapy for most adults with suspected bacterial meningitis,[2] we must determine whether the benefits extend to initial empirical therapy.

Jeffrey A. Tabas, M.D.
Henry F. Chambers, M.D.

San Francisco General Hospital
San Francisco, CA 94110
jtabas@itsa.ucsf.edu

1. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. N Engl J Med 2002;347:1549-56.
2. Tunkel AR, Scheld WM. Corticosteroids for everyone with meningitis? N Engl J Med 2002;347:1613-5.

TO THE EDITOR: Because delaying treatment is associated with worse outcomes,[1] the standard of emergency care in the United States is to administer antibiotics immediately to patients with suspected bacterial meningitis. The results of a culture of cerebrospinal fluid from a subsequent lumbar puncture should not be affected for several hours after the administration of antibiotics.[2]

Given that the interval between the arrival of the patient and the beginning of treatment probably varied and that the time to treatment may affect the outcome, it is disturbing that de Gans and van de Beek did not provide a record of time to treatment. In the absence of such data, one is left to wonder whether statistically significant differences in the time to treatment between the dexamethasone group and the placebo group might help to account for differences in outcome between the groups. Evidence of unusual delay would raise questions about the conclusions of the study.

David N. Tancredi, M.D.
William D. Binder, M.D.

Massachusetts General Hospital
Boston, MA 02114
dtancredi@partners.org

1. Aronin SI, Peduzzi P, Quagliarello VJ. Community-acquired bacterial meningitis: risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Intern Med 1998;129:862-9.
2. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Engl J Med 1997;336:708-16.

TO THE EDITOR: The study by de Gans and van de Beek and their colleagues provides important data on the use of dexamethasone in patients with acute bacterial meningitis. All pneumococci isolated in this study were sensitive to penicillin, although in many areas of the world, the reality is unfortunately different. A big issue of concern is the possibility of a negative interaction between dexamethasone and vancomycin in patients who require treatment with the latter drug.[1] Thus, we might see more therapeutic failures with broader use of dexamethasone therapy. Vancomycin has been considered to be the best treatment for meningitis caused by pneumococci with reduced sensibility to cephalosporins. In spite of the widespread recommendation for its use, there is relatively little clinical research on vancomycin for