Lancet Withdraws Article on Vaccine's Safety

BY JOYCE FRIEDEN

The U.K. medical journal the Lancet has taken the unusual step of withdrawing an article it published—a study of 12 children with behavioral disorders that developed following administration of vaccines or the onset of measles or otitis media.

"Following the judgment of the U.K. General Medical Council [GMC] Fitness to Practise Panel on Jan. 28, 2010, it has become clear that several elements of the 1998 paper by Wakefield et al. are incorrect, contrary to the findings of an earlier investigation," the Lancet editors said in a statement. "In particular, the claims in the original paper that children were 'consecutively referred' and that investigations were 'approved' by the local ethics committee have been proven to be false. Therefore we fully retract this paper from the published record."

The Wakefield study involved 12 children described in the journal as having been consecutively referred to the pediatric gastroenterology department at the Royal Free Hospital and School of Medicine in London (Lancet 1998;351:637-41). All had a history of a pervasive developmental disorder with loss of acquired skills. They also had intestinal symptoms, including diarrhea, abdominal pain, bloating, and food intolerance. "Investigations were approved by the Ethical Practices Committee of the Royal Free Hospital NHS Trust, and parents gave informed consent," the authors wrote.

The researchers took histories, including details of immunizations and exposure to infectious diseases as well as developmental histories.

They also performed a battery of tests, including colonoscopy with multiple biopsies, cerebral MRI, and EEG. Lab tests were performed to rule out known causes of childhood neurodegenerative disorders.

No subjects were found to have neurological abnormalities on clinical examination; all MRI scans, EEGs, and cerebrospinal-fluid profiles were normal, and none of the boys had fragile X syndrome.

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Early development milestones had been achieved by 11 of 12 children, with the exception of one girl found to have coarctation of the aorta and who progressed rapidly after that condition was corrected at 14 months.

Behavioral diagnoses for the children included autism (9), possible postviral or vaccinal encephalitis (2) and disintegrative psychosis (1).

In eight children, parents or physicians linked the onset of behavioral problems to receiving the MMR vaccine. Five children had immediate adverse vaccine reactions including rash, fever, delirium, and in three cases, convulsions.

One subject had received monovalent measles vaccine at 15 months, after which his development slowed. He later received a dose of the MMR vaccine at age 4 years 5 months, a day after which his mother described "striking deterioration in his behavior that she did link with the immunization," the researchers noted.

On endoscopy, the caecum was seen in all cases, and the ileum in all but two. Four cases showed the "red halo" sign around swollen caecal lymphoid follicles, an early endoscopic feature of Crohn's disease. The researchers said the "most striking and consistent feature" was lymphoid nodular hyperplasia of the terminal ileum in 10 subjects.

The researchers noted that "intestinal and behavioral pathologies may have occurred together by chance, reflecting a selection bias in a self-referred group; however, the uniformity of the intestinal pathological changes and the fact that previous studies have found intestinal dysfunction in children with autistic spectrum disorders suggests that the con-

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nection is real and reflects a unique disease process."

Despite consistent gastrointestinal findings, behavioral changes in these children were not consistent, the authors wrote. "In some cases the onset and course of behavioral regression was precipitous, with children losing all communication skills over a few weeks to months."

They added that their study "did not prove an association between measles, mumps, and rubella vaccine and the syndrome described… . If there is a causal link between measles, mumps, and rubella vaccine and this syndrome, a rising incidence might be anticipated after the introduction of this vaccine in the [United Kingdom] in 1988. Published evidence is inadequate to show whether there is a change in incidence or a link with measles, mumps, and rubella vaccine."

According to its report, the GMC panel found that in 1996, Dr. Wakefield was involved in advising Richard Barr, an attorney acting on behalf of people alleged to have suffered harm caused by the administration of the MMR vaccine, "as to the research that would be required to establish that the vaccine was causing injury." The panel found that "[Dr. Wakefield's] involvement in the MMR litigation … had ethical implications and should have been disclosed."

Similarly, it found that Dr. Wakefield should have disclosed that he received 50,000 pounds ($78,000) in funding for the study from the Legal Aid Board—from a grant that Mr. Barr applied for. In helping Mr. Barr apply for the money, Dr. Wakefield did not disclose to the Legal Aid Board that some of the items that money was being requested for, such as MRI studies, were already being paid for by Britain's National Health Service, the board found.

Regarding the Lancet paper, the panel found that Dr. Wakefield's describing the referral process as "routine" when some of the patients were actually specifically selected for the study "was irresponsible and misleading and contrary to [his] duty as a senior author."

The panel also noted that four of the children in the study lacked a history of gastrointestinal symptoms, thereby making them unlikely "routine referrals" to the hospital's gastroenterology department, and that Dr. Wakefield should have disclosed to the Lancet that in 1997, he filed for a patent on a new MMR vaccine.

In the case of one of the children in the study, the panel also found that Dr. Wakefield "ordered the neurophysiological investigations without having requisite paediatric qualifications and writing an incorrect diagnosis on the investigation form."

The panel also noted that Dr. Wakefield paid some children who were guests at his son's birthday party £5 ($8) to have their blood taken as part of the study; it noted that this showed "a callous disregard for the distress and pain that [Dr. Wakefield] knew or ought to have known the children involved might suffer."

In addition to its statement on the withdrawal of the article, the Lancet's editors also released a 2004 comment from the Royal Free and University College Medical School and the Royal Free Hampstead NHS Trust stating that they were "entirely satisfied that the investigations performed on the children reported in the Lancet paper had been subjected to appropriate and rigorous ethical scrutiny. Because the nature of the condition affecting child behavior and gastroenterological symptoms was unknown and required elucidation, the investigation of these children was properly submitted to and fully discussed by the Ethical Practices Committee at the Royal Free Hampstead in 1996… . The clinical management and investigation of these children was performed at the Free by a dedicated team of consultant pediatric gastroenterologists, in full consultation with and agreement of the parents of the affected children" (Lancet 2004;363:824).

Does The Lancet's withdrawal of the paper help vaccination advocates? "I think the retraction is far too little far too late," Dr. Paul Offit, chief of the division of infectious diseases and the director of the Vaccine Education Center at the Children's Hospital of Philadelphia, said in an interview.

"The Lancet published a hypothesis that was unsupported and has since been disproven by careful scientific study. But there is no undoing the harm of that original paper. Many parents abandoned the MMR vaccine. As a consequence, hundreds of children were hospitalized and four were killed by measles. This retraction will do nothing to change that," Dr. Offit continued.

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