



This Week in the Journal

November 7, 2002

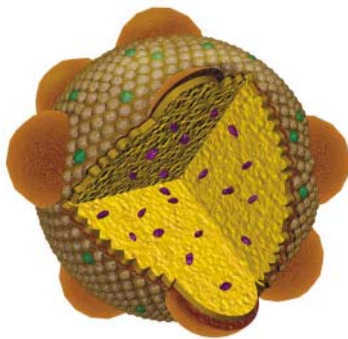
“The risk of autism was similar in vaccinated and unvaccinated children.”

Autism and Measles, Mumps, and Rubella Vaccination

The measles, mumps, and rubella (MMR) vaccine contains a live, attenuated measles virus, and there have been claims that the vaccine is a cause of autism in young children. This study included all children born in Denmark from 1991 through 1998. Using national-registry data on autistic disorders, the investigators found no association between MMR vaccination and a subsequent diagnosis of autism (relative risk, 0.92; 95 percent confidence interval, 0.68 to 1.24) or a related disorder (relative risk, 0.83; 95 percent confidence interval, 0.65 to 1.07).

This national cohort study, which included 537,303 children, obviated the problems of selection bias and misclassification bias. The results provide strong evidence that MMR vaccination is not a cause of autism.

see page 1477 (Perspective, page 1474)



Lipoprotein particle.

Effects of the Amount and Intensity of Exercise on Lipoproteins

Regular exercise has well-established health benefits, some of which are mediated through changes in plasma lipoproteins. This study investigated the relative importance of the amount and the intensity of regular exercise in producing changes in plasma lipoproteins. The amount of exercise per week proved to have a greater effect on lipoproteins than did the intensity of exercise.

The important public health message is that exercise equivalent to jogging 17 to 18 miles per week at a moderate pace is sufficient to produce clinically meaningful changes in plasma lipoproteins. A lower amount of equally intense exercise is not as beneficial.

see page 1483 (editorial, page 1522)

PERSPECTIVE

Suspicious about the Safety of Vaccines

Vaccines represent one of the most effective interventions in medicine. They can protect whole populations from potentially dangerous diseases. Because vaccines are usually given to healthy people, especially children, any concern about the safety of vaccines has to be taken very seriously. Even with close scrutiny, the overall safety record of vaccines is extraordinarily good.

Despite this safety record, for a surprising number of vaccines, there have been widely publicized but unsubstantiated claims of adverse effects (see Table). When suspicions about a vaccine begin to spread, there may be dangerous consequences for the public health. Such is currently the case with the live attenuated measles virus in the vaccine against measles, mumps, and rubella (MMR), which some people erroneously believe is a cause of autism.

Vaccines can cause serious adverse reactions. Documented examples include paralytic disease from the live polio vaccine and intestinal obstruction from the rotavirus vaccine. When these problems occurred, they were recognized and addressed. Because of fears of bioterrorism and smallpox, it is possible that vaccinia vaccination may resume. The live-virus vaccinia vaccine causes many adverse reactions, including rare but severe, or even fatal, infectious complications.

Concern about autism and the measles component of the MMR vaccine began with the awareness that encephalitis is a rare but devastating complication of measles. Some survivors of measles have im-

Examples of Unsubstantiated Claims Made about Some Vaccines.	
VACCINE	UNSUBSTANTIATED ADVERSE EFFECTS
Measles vaccine	Autism and related developmental disorders
Diphtheria–pertussis–tetanus vaccine	Sudden infant death syndrome; epilepsy
<i>Haemophilus influenzae</i> type b	Diabetes mellitus
Inactivated polio vaccine	Paralytic poliomyelitis; simian virus 40 infection
Hepatitis B vaccine	Multiple sclerosis
Anthrax vaccine	Fatigue; Gulf War syndrome
Lyme disease vaccine	Chronic inflammatory arthritis
“Hot lots” (some batches of any vaccine)	Multiple systemic problems
Multiple vaccinations	Undefined harmful immunologic effects from vaccine interactions

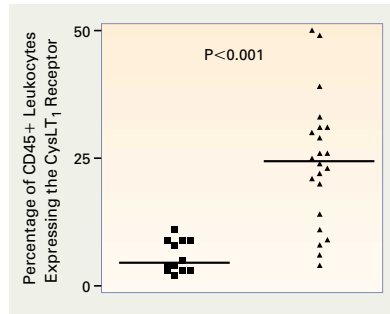
mune-mediated postinfectious encephalomyelitis with seizures and mental retardation. The hypothesis about the measles vaccine and autism also rests in part on some widely publicized research involving a small number of young children with chronic gastrointestinal symptoms and behavioral abnormalities. The researchers speculated on a causal relation among MMR vaccination, abnormalities in lymphoid tissue, and developmental disorders such as autism. Together, these findings have led some to conclude that the measles virus in the MMR vaccine is a cause of autism in children.

When a child has autism, the parents begin to notice problems during the second and third years of life. Sometimes, there is severe regression in language and social skills in young children who initially seemed to be developing quite normally. Since the MMR vaccine is given at the beginning of the second year of life, there is a temporal association between vaccination and the recognition of autism. The situation is further complicated because the frequency of autism appears to have increased by at least a factor of five during the past 20

years. This increase is probably the result of better reporting and wider use of this diagnosis to describe children with unexplained cognitive and behavioral disorders. However, fears only grow when there appears to be an increase in the prevalence of a severe and unexplained disease in children.

A report in this issue of the *Journal* (pages 1477–1482) provides an objective analysis of the rates of autism in relation to MMR-vaccination status in a well-defined population of more than half a million children in Denmark, about one fifth of whom had not received the MMR vaccine. This careful and convincing study shows that there is no association between autism and MMR vaccination. Other studies have also found no such association.

Unfortunately, objective data are not likely to put an end to the controversy. Strongly held beliefs are difficult to change. We live in an era in which the public does not have a high degree of trust in the vaccine manufacturers, the government, or the medical establishment. Consumers have become highly sensitive about safety, and their confidence has not been bolstered by



Cysteinyl Leukotriene Receptor and Aspirin Sensitivity

Patients who are hypersensitive to aspirin have asthma, rhinosinusitis, and nasal polyposis. These findings have been attributed in part to the action of the cysteinyl leukotrienes at one of their receptors. Although aspirin can initiate the reaction, it can also be an effective treatment, since long-term exposure to aspirin leads to a desensitized state. In this study, the authors show that patients with aspirin-sensitive rhinosinusitis have enhanced expression of the cysteinyl leukotriene receptor CysLT₁ on inflammatory cells in nasal-biopsy specimens and that desensitization with aspirin is associated with decreased expression of this receptor on these cells.

Although these data elucidate another key piece in the puzzle of aspirin sensitivity, the story is not complete. The links between aspirin-regulated expression of the CysLT₁ receptor on inflammatory cells and the clinical manifestations of aspirin sensitivity are still speculative.

see page 1493 (editorial, page 1524)

recent recalls of approved drugs or by controversies such as that over mercury-containing preservatives in vaccines (thimerosal, which has now been removed). The large number of approved vaccines and the laws that require vaccination for school entry only increase the tension. Some anti-vaccine groups have received wide publicity, and they try to convince worried parents that avoiding vaccination is “playing it safe.” Internet sites are filled with accusations about damage from the MMR vaccine and other vaccines. Some parents tell moving stories about their children who showed the first signs of autism in the months after vaccination. Such experiences have already led to congressional hearings. But however painful these stories may be, anecdotes are not proof. The association of autism with MMR vaccination appears to be only a predictable coincidence, since nearly 90 percent of children in this country re-

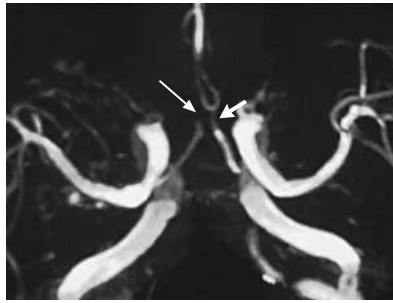
ceive the MMR vaccine at about 15 months of age.

Unsubstantiated accusations that a vaccine causes harm can have serious consequences. Some people begin to avoid vaccination, increasing the number at risk, particularly in communities where anti-vaccine activists are most successful. Once a vaccine has been tied repeatedly to even an unsupported claim of an adverse effect, costly legal action usually follows, even if the vaccine is eventually proved to be safe. The companies that produce vaccines come to associate vaccines with adverse economic effects for themselves, with little profit and huge liability. Effective vaccines may be withdrawn from the market. It becomes harder to run vaccination programs, including those in developing countries where the needs are greatest.

Those arguing against vaccination forget how bad the illnesses and their complications can be. They

forget that in this country before the development of the measles vaccine, thousands of children had severe illness from measles, sometimes resulting in permanent disability. In 1960, 400 children died from measles. But the biggest tragedy is that outside of the developed countries, more than a million children still die from this disease each year. Those deaths are preventable by a measles vaccine that is cost effective and safe. Children everywhere deserve the protection that carefully developed, carefully monitored vaccines can provide against so much disease.

EDWARD W. CAMPION, M.D.



Brief Report: Vasculopathy Due to Varicella–Zoster Virus

Several months after having zoster on the sacrum, a 71-year-old man had a transient ischemic attack with occlusion of the right anterior cerebral artery. Six months after having zoster in the ophthalmic distribution, a 76-year-old woman had sudden loss of vision in the left eye. In both cases, the acute vascular events were caused by the varicella–zoster virus, and in both, the deficits resolved after intravenous treatment with acyclovir.

see page 1500

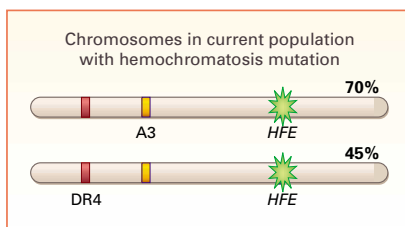
“An estimated 19.2 million adults in the United States have stage 1, 2, 3, or 4 kidney disease.”

Clinical Practice: Nondiabetic Kidney Disease

A 66-year-old man without diabetes has worsening hypertension. He has a serum creatinine level of 1.8 mg per deciliter (159 μ mol per liter), proteinuria (2+), and a fasting serum low-density lipoprotein cholesterol level of 140 mg per deciliter (3.6 mmol per liter). He smokes half a pack of cigarettes per day. Ultrasonography reveals small, symmetric kidneys without hydronephrosis or cysts. How should this patient be evaluated and treated to slow the progression of kidney disease?

This article reviews the classification of nondiabetic kidney disease and approaches to slowing disease progression.

see page 1505



Genomic Medicine: Genomic Medicine — A Primer

This review article launches our series on genomic medicine. It provides definitions of terms commonly used in genetics, delineates the distinction between genetics and genomics, and supplies examples of the ways in which genetic information can be used in the day-to-day care of patients. The mechanisms leading to the availability of more than 100,000 proteins from only approximately 30,000 genes are described. The various common types of mutations are identified and defined, and modes of inheritance — from simple mendelian to complex to mitochondrial — are detailed.

see page 1512 (editorial, page 1526)