

I was therefore concerned when I read the sections concerning research on embryonic stem cells in the drafts of the report and the final Report on Monitoring Stem Cell Research. Work with animal models has been indicating the potential benefits of research involving embryonic stem cells for more than two decades. More recently, research breakthroughs in the generation and differentiation of human embryonic stem cells and increased understanding of these processes have suggested that this avenue of research will eventually lead to beneficial uses in health care. Work with animal models increasingly suggests that such research may result in therapies for diabetes, Parkinson's disease, and spinal injuries, among other conditions. Yet the best possible scientific information was not incorporated and communicated clearly in the council's report, suggesting that the presentation was biased.

How might perceived bias in a federal commission such as the bioethics council affect the ability of the nation to receive the best available scientific information on which to base policy decisions? Will researchers be unwilling to provide their expert opinions regarding their field of research for fear that they will be used to promote a particular view held by the council? I am afraid that this effect is already occurring. I was recently contacted by a world leader in research involving neural stem cells from adults; he was considering withdrawing his agreement to provide his expert opinion to the council, for fear that the potential of research involving adult stem cells would be overstated as a justification for a continued ban

on federal funding for promising research on embryonic stem cells.

When prominent scientists must fear that descriptions of their research will be misrepresented and misused by their government to advance political ends, something is deeply wrong. Leading scientists are routinely called on to volunteer their expertise to the government, through study sections of the National Institutes of Health and advisory panels of the National Academy of Sciences and as advisers to departments ranging from health and human services to defense. It has been the unspoken attitude of the scientific community that it is our duty to serve our government in this manner, independent of our personal political affiliations and those of the administration in effect at the time. But something has changed. The healthy skepticism of scientists has turned to cynicism. There is a growing sense that scientific research — which, after all, is defined by the quest for truth — is being manipulated for political ends. There is evidence that such manipulation is being achieved through the stacking of the membership of advisory bodies and through the delay and misrepresentation of their reports. As a naturalized citizen of the United States, I have an immigrant's love for my country. But our country must not fail us. Scientific advice should and must be protected from the influence of politics. Will the President's Council on Bioethics be up to that challenge?

This article was published at [www.nejm.org](http://www.nejm.org) on March 12, 2004.

From the University of California, San Francisco, School of Medicine.

## Childhood Immunizations and Chronic Illness

Lynne L. Levitsky, M.D.

A hundred thousand persons, upon the smallest computation, have been inoculated in these realms. The number who have partaken of its benefits throughout Europe and other parts of the globe are incalculable; and it now becomes too manifest to admit of controversy, that the annihilation of the Small Pox, the most dreadful scourge of the human species, must be the final result of this practice.

— Edward Jenner, *The Origin of the Vaccine Inoculation*, 1801

These hopeful words of Edward Jenner (see Figure) were prescient, although their promise remained unfulfilled for almost 200 years. One hundred years ago, more than 48,000 people contracted smallpox annually in the United States. Today, smallpox has been eradicated worldwide, and the virus can be found only in the freezers of a few selected laboratories. Because of mass immunization, other diseases associated with very high morbidity and mortality have also been virtually eradicated in this country. In 2001, only 2 cases of diphtheria, none of paralytic poliomyelitis, and 116 of measles were reported.

Before the availability of vaccines, there were more than 170,000 cases of diphtheria, 16,000 of paralytic poliomyelitis, and 500,000 of measles in the United States each year.<sup>1</sup> Immunization prevents disease in individual children, reduces the burden of disease in the population, and can create herd immunity, preventing the further spread of devastating disease. The ultimate public health purpose of immunization is the total elimination of both an infectious disease and the need for vaccination against it. Only in the case of smallpox has it been possible to achieve this goal.

However, immunization has not been entirely without risk. Some vaccines introduced in the past 40 years have been associated with unexpected adverse reactions. A rotavirus vaccine was recalled because of an association with an increase in the rate of intussusception, and a mutated oral poliovirus vaccine caused sporadic paralytic poliomyelitis. Public health interventions always carry the potential for risk. It is important to document that any small risk to individual vaccinees is outweighed by both the potential for benefit to each vaccinee and the potential for disease prevention in the population as a whole.

We have traded the morbidity and mortality associated with many acute, infectious childhood diseases for the morbidity and mortality associated with more chronic disorders whose causes are as yet uncertain. Infants immunized according to the current consensus guidelines have received up to 18 separate injections for protection against 12 different infectious diseases by the time they reach two years of age.<sup>1</sup> Given the close temporal relationship between frequent immunizations and the onset of some chronic childhood illnesses, it is not surprising that speculation and epidemiologic studies have attempted to link chronic disorders of childhood to immunizations. The discussions about postulated links to the increased incidence of autism and type 1 diabetes mellitus in childhood have been particularly contentious. Concern about the deleterious effect of immunizations has focused on potential adverse immunologic responses to killed vaccines, possibly harmful components of adjuvants or vehicles in vaccines, and untoward responses to live viral vaccines. There is now sufficient information to permit us to comment on each of these mechanisms.

Adverse responses to killed vaccines have included prolonged crying, fever, fussiness, and rare febrile seizures in up to 1 percent of children who receive the combination diphtheria–tetanus–acellular pertussis vaccine. Serious reactions have been more frequent with the whole-cell pertussis vaccine prep-

aration than with the acellular vaccine whose use is recommended today. However, each year, a small number of children who receive the current acellular pertussis vaccine have a more serious reaction, such as prolonged seizure, coma, or shock. Components of the vaccine have included organic compounds such as formaldehyde, human albumin, egg proteins, antibiotics, yeast proteins, aluminum, and thimerosal, a preservative containing ethyl mercury. Occasionally, allergic reactions to these organic compounds have been reported. However, aluminum is a naturally occurring environmental contaminant, and the aluminum burden in vaccines is lower than that found in breast milk or formula. Because mercury toxicity causes neurologic damage, the presence of organic mercury in several common vaccines has aroused particular concern. Although the amounts of organic mercury administered during immunization were within the range that is considered potentially hazardous, ethyl mercury is excreted rapidly and does not seem to accumulate after the administration of vaccine. A proposed link to autism has not been substantiated by several careful epidemiologic studies, yet widely publicized parental concern persists. Since 2001, vaccines used in the United States have not contained thimerosal. Therefore, a review of the incidence of autism over the next few years should definitively address these remaining concerns.<sup>2,3</sup>

Although very effective at preventing poliomyelitis in immunocompetent people and also effective in ensuring the spread of herd immunity, live oral poliovirus vaccine posed a risk to immunocompromised people. Killed poliovirus vaccine is currently recommended for all children. It has been suggested that live attenuated vaccines, such as that used for



**Figure. Dr. Jenner Performing His First Vaccination, 1796.**  
Oil painting by Ernest Board. Courtesy of Wellcome Library, London.

measles, mumps, and rubella, are powerful modifiers of the immune response and might be related to the onset of several autoimmune disorders, including type 1 diabetes. However, the link between vaccination and subsequent autoimmune disorders has not been strong.

Diabetes now frequently develops at younger ages, and it has been argued that the total incidence of type 1 diabetes is increasing and that high socioeconomic status, a cleaner environment, and a decreasing frequency of infections may play a role. These factors, in turn, are correlated with increasing immunization coverage. Small studies have suggested possible relationships between the onset of diabetes and immunizations. However, these studies have not been supported by more rigorous epidemiologic examinations.<sup>4,5</sup> In this issue of the *Journal*, Hviid and colleagues (pages 1398–1404) report a retrospective review of a cohort of Danish children born between 1990 and 2000; they conclusively demonstrate that there is no relationship between vaccination history and the development of type 1 diabetes. Neither the administration of live attenuated vaccines nor the administration of killed

vaccines was correlated with the development of type 1 diabetes in a relatively high-risk Scandinavian population. This study will, one hopes, be the last one that is necessary to disprove an association between immunization and diabetes. The scientific community should now move on to the most important tasks: identifying the genetic, immunologic, and environmental phenomena that are actually responsible for the development of diabetes and finding the means to prevent and treat this chronic disorder.

From the Pediatric Endocrine Unit, Massachusetts General Hospital and Harvard Medical School, Boston.

1. Pickering LK, ed. Red book: 2003 report of the Committee on Infectious Diseases. 26th ed. Elk Grove Village, Ill.: American Academy of Pediatrics, 2003.
2. Nelson KB, Bauman ML. Thimerosal and autism? *Pediatrics* 2003;111:674-9.
3. Madsen KM, Lauritsen MB, Pedersen CB, et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics* 2003;112:604-6.
4. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001;358:221-9. [Erratum, *Lancet* 2001;358:766.]
5. Offitt PA, Hackett CJ. Addressing parents' concerns: do vaccines cause allergic or autoimmune diseases? *Pediatrics* 2003; 111:653-9.

## The White Lesion That Kills — Aneuploid Dysplastic Oral Leukoplakia

Deborah Greenspan, B.D.S., D.Sc., and Richard C.K. Jordan, D.D.S., Ph.D.

Perhaps the earliest link between oral leukoplakia and cancer was made by James Paget, for whom Paget's disease was named; he also recognized the connection between oral leukoplakia and smoking. Leukoplakia is a clinical term that refers to an oral mucosal white patch that will not rub off and is not attributable to any other known disease. It is considered to be potentially malignant, with a transformation rate in various studies and locations ranging from 0.6 to 18 percent. Clinically, oral leukoplakia is in the same spectrum of disease as the more sinister red or speckled lesion erythroplakia, which has a much higher transformation rate and is more often found on biopsy to be squamous-cell carcinoma.

The leukoplakia we are discussing here should be distinguished from oral hairy leukoplakia, the lesion associated with Epstein-Barr virus and seen in immunosuppressed persons, predominantly but

not exclusively those with human immunodeficiency virus infection. White patches in the mouth may have other causes, including chronic trauma such as friction and mucocutaneous diseases such as white sponge nevus, lichen planus, or lupus erythematosus. However, the lesion that is the subject of the article by Sudbø et al. in this issue of the *Journal* (pages 1405–1413) is more commonly associated with tobacco-related habits— notably, smoking and the use of some other forms of tobacco, including moist snuff (smokeless tobacco) and pan (betel nut). Another form of precancer, proliferative verrucous leukoplakia, is predominantly found in those who do not use tobacco, but it has a high rate of transformation to cancer.

Here is where the histopathological changes known as dysplasia enter the picture. On biopsy, most leukoplakias show histologic features of epi-