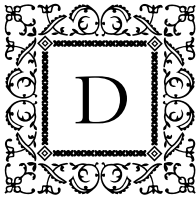


The True Story of Pertussis Vaccination: A Sordid Legacy?

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URING the last half of the twentieth century, pertussis vaccine has been at the center of controversies over the evaluation and marketing of vaccines for children. This controversy has transcended the simple confines of scientific research to redefine relationships among industry, government, law, and consumer advocacy. The dangerous side effects of whole-cell pertussis vaccine have been known for at least the last five decades, and for the last four a safer alternative has been available. But not until the late 1990s has that safer alternative become routine for American children. This paper explains why and how this transformation in care took place. We were part of the transformation, supporting the advocates for the new, acellular vaccine with scientific testimony. Although our appearance in this story takes place in the 1980s, the history of the vaccine began much earlier in the twentieth century.

Even though there was incidental medical evidence as early as the 1930s and clear-cut evidence by the 1950s that whole-cell pertussis vaccine caused neurological sequelae, American pharmaceutical companies by and large persisted in marketing whole-cell vaccines until the end of 2000 because the acellular versions, in their opinion, were too costly to produce, test, and sell. Nevertheless, U.S. manufacturers were granted at least one patent in every decade since the 1920s to produce acellular pertussis vaccines, and several countries either legislated the use of the acellular form only or stopped using pertussis vaccination altogether. Change finally began in the United States in

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the 1990s and was completed by 2000, largely because of the combined pressures of litigation and political action on the part of groups of parents whose children were damaged by the whole-cell vaccines. These groups pressured the federal government to study and ameliorate the adverse effects of the vaccine, but the federal government was also pressured by vaccine producers for protection from the potentially large numbers of highly expensive civil lawsuits brought by parents. These pressures culminated in the passage of a compensation act and the charging of the U.S. Institute of Medicine (IOM) of the National Academy of Sciences to make recommendations for solving the problem. This ultimately led to the licensing and recommendation of acellular pertussis vaccine for booster shots beginning in 1992 and for all shots given beginning in 1996. By the end of 2000, U.S. manufacturers had stopped making whole-cell pertussis vaccine for use in the United States.

In this detailed history of the topic, we first describe the infectious disease pertussis and the story of the vaccines produced to prevent it. We then consider the history of scientific knowledge about the myriad adverse reactions that have been observed following vaccination—from mild fevers to seizures, encephalopathy, permanent brain damage, and even death. We review the history of the scientific advances that allowed production of a far safer and more effective vaccine. Finally, we explore the history of the industrial, monetary, political, legal, and consumer factors that finally led to the use of the safer vaccine for all U.S. children as well as the work that still needs to be done to provide it to children around the world.

THE SCOURGE OF PERTUSSIS

Pertussis, commonly called whooping cough, is a bacterial infection that usually strikes its victims with initially mild symptoms, resulting in an incubation time for the disease that is hard to determine but is usually estimated to be from six to twenty days, with a mean of seven days. As the disease progresses the symptoms become more pronounced, with coughing episodes occurring ten to twenty-five times a day as a means to expel accumulated mucus blocking the airway. After the mucus is expelled, the victim's breathing is labored due to swollen and irritated air passages, which results in the production of a whooping sound with every inhalation. The disease severely affects the nutrition and hydration of its victims. The cough causes

hemorrhages on various portions of the body, herniae, emphysema, and pneumothorax. Additionally, the disease in its most severe forms can cause seizures, encephalopathy, and even death. Recovery from the disease is characterized by a decreasing frequency of coughing episodes and a general increase in wellness. However, this usually requires many weeks—a characteristic reflected in the Japanese and Chinese name for pertussis: the 100-day cough.¹

Pertussis is an epidemic disease, occurring every 2 to 5 years in endemic areas, with an average interval of 3.3 years. It is highly infectious; attack rates in nonimmunized populations have been reported to range from 25 to 50 percent in schools and from 70 to 100 percent in susceptible household contacts. Based on data from a large series of children hospitalized for pertussis, it has been estimated that 1.7 to 7 percent or more of its victims will develop central nervous system complications. The incidence rates of encephalopathy ranged from an estimated 0.08 per 1,000 cases from 1932 to 1946 in Brooklyn, New York, to 0.8 per 1,000 cases in the National Encephalopathy Study.²

Our earliest recorded description of pertussis comes from a 1578 record by Guilanne de Baillon:

The lung is so irritated by every attempt to expel that which is causing the trouble it neither admits the air nor again easily expels it. The patient is seen to well up and as if strangled holds his breath tightly in the middle of the throat . . . For they are without the troublesome coughing for the space of four or five hours at a time, then this paroxysm of coughing returns, now so severe that blood is expelled with force through the nose and through the mouth. Most frequently an upset stomach follows . . . For we have seen so many coughing in such a manner, in whom after a vain attempt semi-putrid matter in an incredible quantity was ejected.³

Unlike many bacterial diseases, in whooping cough the organism does not invade the entire body but is localized in the lining of the lungs. The most severe symptoms are caused by the poison the bacteria

1. J. H. Lapin, *Whooping Cough* (Springfield, Ill.: Thomas Publishing, 1943); A. T. Wilson, I. R. Henderson, E. J. H. Moore, and S. N. Heywood, "Whooping-cough: Difficulties in Diagnosis and Ineffectiveness of Immunization," *Br. Med. J.*, 1965, 2, 623-26; L. C. Olson, "Pertussis," *Medicine*, 1975, 54, 427-69; F. F. Cartwright, *Disease and History* (New York: Dorset Press, 1972).

2. U.S. Institute of Medicine, *Adverse Events Associated with Pertussis and Rubella Vaccines* (Washington, D.C.: National Academy Press, 1991).

3. Quoted in W. H. Holmes, *Bacillary and Rickettsial Infections* (New York: The Macmillan Co., 1940).

secrete, called pertussis toxin, which has a wide variety of effects in patients. It sensitizes them to the effects of histamine through a biological marker called histamine-sensitizing factor (HSF). Another component, islet-activating factor (IAF), causes a rise in insulin secretion and a consequent fall in blood sugar. This can cause brain damage if it is too extreme because the brain is solely dependent on sugar for its energy. Pertussis toxin includes leukocyte-promoting factor (LPF), which raises white blood cell counts. The toxin lowers the blood-brain barrier, allowing various other toxins and viruses to enter the brain. And pertussis toxin itself is a known neurotoxin. Finally, pertussis bacteria make an exotoxin called adenyl cyclase, which adversely affects neurotransmitters.

Because the symptoms of whooping cough are caused primarily by pertussis toxin, one of the main mechanisms by which pertussis vaccines protect against whooping cough is by causing the body to produce antibodies that inactivate the toxin. Because some exposure to the toxin is required to achieve this effect, the toxin itself is included in most pertussis vaccines. This can cause problems if it is included in active form, as it is in whole-cell pertussis vaccine. The problems that result are similar to the clinical symptoms of pertussis infection, though they occur to a lesser degree. There is, however, a way to neutralize this potentially dangerous toxin chemically or by genetic engineering so as to render it inactive while maintaining its antigenic properties. The currently used acellular vaccine accomplishes this by mildly damaging the pertussis toxin with formaldehyde.⁴

EARLY VACCINE WORK

The development of a vaccine against pertussis first became possible when the bacterium *Bordetella pertussis* was grown in the laboratory. Jules Bordet and Octave Gengou of the Pasteur Institute of Brussels developed the initial technique in 1906 after more than twenty years of work by a considerable number of investigators.⁵ The development of this technique led to a wave of empirical research attempting to produce a pertussis vaccine by culturing the bacteria on BG agar

4. R. D. Sekura, J. Moss, and M. Vaughan, *Pertussis Toxin* (New York: Academic Press, 1985).

5. J. Bordet and O. Gengou, "Le Microbe de la Coqueluche," *Annales de l'Institut Pasteur*, 1906, 20, 731-41; Bordet and Gengou, "Note Complémentaire sur le Microbe de la Coqueluche," *Ann. de l'Institut Pasteur*, 1907, 21, 720-32; Bordet and Gengou, "L'endotoxine Coquelucheuse," *Ann. de l'Institut Pasteur*, 1909, 23, 415-19.

plates (named for Bordet and Gengou) and then inactivating the bacteria and toxicity by physical and chemical procedures. The individuals associated with this research included Bordet and Gengou in 1912, Charles Nicolle of the Pasteur Institute of Tunis in 1913, and Thorvald Madsen of the Danish State Serum Institute in Copenhagen in 1914, among others.⁶

The first challenge these researchers faced was to establish the efficacy of the vaccines produced, a task that was complicated by the facts that much of the older population was already immune to pertussis infection, that there were no laboratory or animal tests in existence at that time to measure how well the new vaccines were working, and that toxicity was difficult to measure because there was no agreement among the scientific community as to the nature of the toxicity. This resulted in all the vaccines produced from the early research falling into one of several groups. There were vaccines that appeared to prevent the disease, but there were questions about their toxicity. There were other vaccines that were so toxic that they could not be used for clinical studies. Finally, there were vaccines that were not toxic but whose disease-fighting ability could not be established.⁷

Despite the difficulties, by 1914 there were six U.S. manufacturers of pertussis vaccine, and pertussis vaccine was listed in “New and Nonofficial Remedies,” published by the American Medical Association (AMA). This document was a listing by the AMA of treatments that had possible efficacy but were not fully proven to work. Pertussis vaccine was removed from this list in 1931 because of equivocal efficacy results, but was readmitted in 1944.⁸ In practice, various presumptive pertussis vaccines were used sporadically with no formal testing between 1914 and 1925. Madsen, in 1925 and later in 1933, was the first to report the results of clinical trials using whole-cell pertussis vaccine during the 1923–1924 whooping cough epidemic in the Faroe Islands of the North Sea. A careful examination was made between vaccinated and unvaccinated individuals who had been exposed to the disease. For the first time, the results were encouraging,

6. A. Chase, *Magic Shots: A Human and Scientific Account of the Long and Continuing Struggle to Eradicate Infectious Diseases by Vaccination* (New York: William and Morrow Co., Inc., 1982).

7. E. M. Sill, “The Vaccine Treatment of Whooping-cough,” *Am. J. Dis. Child.*, 1913, 5, 379–85.

8. H. M. Felton and C. Y. Willard, “The Current Status of Prophylaxis by *Haemophilus pertussis* vaccine,” *J. Am. Med. Assoc.*, 1944, 126, 294–97.

establishing the usefulness of pertussis vaccine as a protective instrument against infection. But there was also evidence that additional work would be needed to develop a more effective vaccine. The study specifically showed that individuals in both the vaccinated and the unvaccinated group developed the disease at the same rate, but among those vaccinated the manifestations of the disease were much milder and hence fewer died.⁹

In a 1929 outbreak of pertussis again in the Faroe Islands, Madsen showed for the first time that the vaccine could be used to help prevent the disease. In his study, pertussis bacteria grown on BG plates with horse blood and killed by mild heat produced a decrease of more than 20 percent in the occurrence of pertussis among vaccinated individuals when compared to those who were unvaccinated. Additionally, as with the previous study, the symptoms that vaccinated individuals developed were much milder, if they did come down with the disease.¹⁰ Although these early vaccine trials successfully helped to control two outbreaks of pertussis, Madsen's 1933 paper also reported two instances of lethal adverse reactions within forty-eight hours of vaccination. Additionally, in that same year, Louis Sauer of Northwestern University Medical School in Chicago described a clinical study in Evanston, Illinois using a pertussis vaccine similar to that of Madsen's trial that showed minor reactions to the vaccine.¹¹

In 1932, Dr. Pearl Kendrick and her associate Dr. Grace Eldering, both of the Michigan Department of Health in Grand Rapids, began working on producing a more effective vaccine against childhood pertussis by growing the bacteria on BG medium plates that contained sheep's blood. The bacteria were then treated with thimerosal and stored at refrigerator temperatures as a means to inactivate them. When the vaccine was subjected to clinical efficacy trials in 1934, Kendrick and Eldering reported positive results.¹² However, a similar study conducted in Cleveland, Ohio, by J. A. Doull (a prominent

9. T. Madsen, "Whooping-cough: Its Bacteriology, Diagnosis, Prevention, and Treatment," *Boston Med. Surg. J.*, 1925, 192, 50-60.

10. T. Madsen, "Vaccination against Whooping-cough," *J. Am. Med. Assoc.*, 1933, 101, 187-88.

11. L. Sauer, "Whooping-cough: A Study in Immunization," *J. Am. Med. Assoc.*, 1933, 101, 239-41; L. Sauer, "Immunization with *Bacillus pertussis* Vaccine," *J. Am. Med. Assoc.*, 1933, 101, 1449-51.

12. P. Kendrick and G. Eldering, "Progress Report on Pertussis Immunization," *Am. J. Public Health*, 1936, 26, 8-12.

epidemiologist) and his colleagues in 1936 showed that the vaccination provided no increased protection over those who remained unvaccinated.¹³ Analyzing these conflicting results, Kendrick, Eldering, and Dr. Margaret Pittman decided that varying numbers of bacteria might be contained in the vaccines, so they developed an optical method known as opacity unitage to test bacterial content. This method correlated the cloudiness of a bacterial suspension with the amount of bacteria the suspension contained.¹⁴

The idea of quantifying the concentration of bacteria was later used to develop another test, this one performed in mice. Known as the mouse potency test, it measured the ability of pertussis vaccine to protect mice from being killed by pertussis infection. All clinical trials conducted in the late 1930s and 1940s used this test as a means of determining the efficacy of new whole-cell pertussis vaccines. On 5 January 1946 the National Institutes of Health (NIH) sent the mouse potency testing method to the fourteen U.S. manufacturers of whole-cell pertussis vaccine, and it became part of the First NIH Minimum Requirements for Pertussis Vaccination in 1949. Three of the manufacturers met the specified potency levels, three manufacturers had products with no demonstrable potency, and there was lot-to-lot variation among the remaining eight manufacturers.¹⁵ Use of the test led to the eventual acceptance by the 1950s of whole-cell pertussis vaccines as the most effective means to prevent the widespread occurrence of the wild-type disease.¹⁶ Meanwhile, trials of pertussis vaccine efficacy in human populations were done over the years, but they were sporadic and the results were highly variable. The scientific community generally accepted, at the time, that whole-cell pertussis vaccines that had passed the mouse potency test were

13. J. A. Doull, G. S. Shibley, and J. S. McClelland, "Active Immunization against Whooping Cough. Interim Report of the Cleveland Experience," *Am. J. Public Health*, 1936, 26, 1097-1105.

14. M. Pittman, "History, Benefits and Limitations of Pyrex Glass Particle Opacity References," *J. Biol. Stand.*, 1976, 4, 115-25.

15. The following memoranda were referenced in M. Pittman, "History, Benefits and Limitations of Pyrex Glass Particle Opacity References," *J. Biol. Stand.*, 1976, 4, 115-25: National Institutes of Health, Memorandum to Manufacturers of Pertussis Vaccine, 1945; National Institutes of Health, *Minimum Requirements: A Tentative Mouse Protection Test for Determining the Antigenicity of Pertussis Vaccine*, 1946; National Institutes of Health, *Minimum Requirements: Pertussis Vaccine*, 1948.

16. Medical Research Council, "The Prevention of Whooping-cough by Vaccination," *Br. Med. J.*, 1951, 2, 1464-72; Medical Research Council, "Vaccination against Whooping-cough," *Br. Med. J.*, 1956, 2, 454-62.

the best way to control pertussis and that any disadvantages were far outweighed by their positive effects.

The effectiveness of the new vaccines was not the only issue that needed to be addressed, however. It was also necessary to measure the toxicity of the vaccines in those who were injected with them. This was done, again using mice as models, in what became known as the mouse toxicity test. This test assesses endotoxin, LPF, and heat labile toxin (HLT). Early mouse deaths in the mouse toxicity test would indicate the presence of biologically active HLT. The degree of weight loss at twenty-four hours is probably an indication of the endotoxin content of the vaccine. A reduced rate of late weight gain is taken to be a measure of the LPF content. At the time that a product license was approved, evidence was presented to show that the method of inactivation used by the manufacturer detoxified the HLT component of pertussis vaccine.¹⁷

Since the 1950s, all whole-cell pertussis vaccines licensed and released in the United States have been required to pass the mouse toxicity test. It was hoped that the introduction of the test would serve to limit the toxicity of whole-cell pertussis vaccine by identifying highly toxic production lots early on and thus preventing their use in humans. Unfortunately, field observations of the toxicity of the vaccines have shown that there is little correlation between the toxicity of a whole-cell pertussis vaccine in humans and the mouse toxicity test.¹⁸ In 1961, Dr. C. N. Christensen, a physician from Eli Lilly and Company, then a whole-cell pertussis producer, was commissioned to study whether the mouse toxicity test had been serving its purpose. The results of his study were conveyed to all manufacturers of whole-cell pertussis vaccine and were presented at the 1963 International Symposium on Pertussis. He concluded: "It is obvious that severe neurologic reactions have occurred in children after immunization with pertussis vaccines which have passed the toxicity and potency tests currently in use . . . It was clear that there was no correlation between the mouse toxicity test and the reaction rates in children."¹⁹

17. U.S. Institute of Medicine, *Adverse Events*.

18. R. M. Barkin and M. E. Pichichero, "Diphtheria-Pertussis-Tetanus Vaccine: Reactogenicity of Commercial Products," *Pediatrics*, 1979, 63, 256-60.

19. C. N. Christensen, "Pertussis Vaccine Encephalopathy," Eli Lilly Report, 1962, 1-5, p. 10. This article is in the authors' possession.

WHOLE-CELL PERTUSSIS VACCINES

The first modern whole-cell pertussis vaccine was put in its currently known form by Kendrick in 1942, combining whole-cell pertussis with toxoided diphtheria and tetanus to form DTP or DPT vaccine. In producing the pertussis component, the toxins were deactivated by exposure to mild heat and then stored in a cold environment with either thimerosal or formalin as preservatives. Thimerosal, which is a mercury derivative, gained precedence over all other preservatives and eventually was used as the preservative of choice in most vaccines (except polio vaccines, since mercury is deleterious to the polio virus).²⁰ The pertussis vaccine produced in this way could be used by itself, but it was often mixed with diphtheria and tetanus toxoids to create the DTP vaccine once commonly given to all American children. The DTP vaccine produced in this way was considered to represent an acceptable compromise between a certain level of toxicity and an effective level of functionality.

However, the toxicity of pertussis vaccine is primarily due to the levels of two poisons: endotoxin and pertussis toxin. The production of whole-cell pertussis vaccine does not inactivate these substances. Therefore, the vaccine has some of the toxic biological activities of the disease itself. Geier and colleagues demonstrated in 1978 that whole-cell pertussis vaccine contained enough endotoxin to be detected by the Limulus endotoxin assay even when diluted 100,000 to 1.²¹ Endotoxin is a highly toxic substance. Doctors and scientists take great care to ensure its absence from most medicines, intravenous tubing, syringes, and other medical instruments before using them. Given the high levels of endotoxin in whole-cell DTP vaccines, it is not surprising that virtually all children who receive the vaccine develop a fever. It is also not surprising that a smaller percentage of children get more severe reactions which may include seizures, shock, collapse, and even death.²² Nevertheless, the dangers posed by the

20. P. Kendrick, G. Eldering, and A. A. Borowski, "A Study of Active Immunization against Pertussis," *Am. J. Hyg.*, 1939, 29, 133-39; R. A. Gardner and M. Pittman, "Relative Stability of Pertussis Vaccine Preserved with Methiolate, Benzethonium Chloride, or the Parabens," *Appl. Microbiol.*, 1965, 4, 564-69.

21. M. R. Geier, H. Stanboro, and C. R. Merrill, "Endotoxin in Commercial Vaccine," *Appl. Environ. Microbiol.*, 1978, 36, 445-49.

22. *Ibid.*

high levels of endotoxin in whole-cell pertussis were overlooked or tolerated due to two factors. First, from the late 1940s until the early 1960s, physicians had no choice but to use whole-cell pertussis vaccine because there was no other type on the market. Second, the vaccine manufacturers hid the fact that their whole-cell pertussis vaccine contained high levels of endotoxin and in fact failed to even mention endotoxin anywhere in their product information.

Despite these inherent difficulties with the whole-cell pertussis component of the DTP vaccine, by the late 1940s every manufacturer had begun using the Kendrick process for producing it. The predecessor of the Food and Drug Administration (FDA), operating without today's rigorous requirements of testing for safety and effectiveness, approved the manufacture and use of whole-cell pertussis vaccine. This official position on whole-cell pertussis vaccine, coupled with the ease of its production and the relative cheapness of the product, caused all of the manufacturers to make the switch to the whole-cell product. Because of all these factors, more and more children began to receive voluntary vaccination for the disease. Additionally, the vaccine manufacturers started lobbying the pediatric societies and the states to require children to be vaccinated against pertussis. By the mid-1960s they had succeeded. Most states had passed laws requiring all children to be vaccinated with the combination DTP vaccine prior to entering school.²³

With this widespread administration of whole-cell DTP vaccination came the first published reports of irreversible brain damage after its administration.²⁴ These reports generated the first warnings that whole-cell pertussis vaccination should not be administered to anyone with a neurological disorder. Clinicians also began reporting on a small number of children each year who were killed by the toxins in the whole-cell pertussis vaccine. In fact, in virtually every year from the early 1950s through the present, at least one article has been published describing similar adverse effects. For example, H. W. Felton and W. F. Verwey reported in 1953 that "virtually every child

23. H. L. Coulter and B. L. Fisher, *DPT: A Shot in the Dark* (San Diego, Calif.: Harcourt Brace Jovanovich, 1985).

24. M. Brody and R. G. Sorley, "Neurological Complications following Administration of Pertussis Vaccine," *N. Y. State J. Med.*, 1947, 47, 1016-17; R. K. Byers and F. C. Moll, "Encephalopathies following Prophylactic Pertussis Vaccination," *Pediatrics*, 1948, 1, 437-57.

who receives pertussis immunization demonstrates some form of systemic toxicity within the 24 hours following injection. . . . If the child survives the typical sequelae of severe generalized episodes, CNS damage often remains.”²⁵ Justus Strom similarly warned in 1960:

In Sweden, as in several other countries, neurological complications after pertussis (triple) vaccinations have been observed. A nationwide investigation showed that 36 cases of such complications had occurred in about 215,000 vaccinated children (one in 6,000) during 1955–8. Most of these consisted of convulsions, coma, or collapse, and the children were restored to health; but there were four deaths, of which two were sudden, and nine cases indicative of encephalopathies with severe lesions (one in 17,000).²⁶

Dr. H. D. Piersma of Wyeth Laboratories, who for many years manufactured whole-cell DPT, admitted during the Proceedings of the 4th International Symposium on Pertussis held at the NIH in 1963 that there was general agreement among clinicians that use of pertussis vaccine was occasionally accompanied by unfavorable reactions. Certain of these reactions were severe and resulted in permanent damage to the CNS.²⁷ Margaret Haire and colleagues in 1967 likewise concluded, “it is well known that they [whole-cell DTP vaccinations] cause reactions in many of the infants who receive them. These reactions, which are largely attributed to the pertussis component, vary from slight pyrexia and fretfulness, which are extremely common, to serious and sometimes fatal encephalopathy, which is fortunately exceedingly rare.”²⁸ Criticism of whole-cell pertussis vaccine continued during the 1970s.²⁹ In 1980, O. T. S. Bajc persisted in observing that “since there is a significant difference between the incidence of spontaneous fits in children of the same age group and the incidence after DPT, a causal relationship between the DPT and the seizures appears to be confirmed. . . . the severe

25. H. M. Felton and W. F. Verwey, “The Epidemiological Value of a Non-cellular Pertussis Antigen,” *Pediatrics*, 1953, 16, 637–50, p. 12.

26. J. Strom, “Is Universal Vaccination against Pertussis Always Justified?” *Br. Med. J.*, 1960, 2, 1184–86, p. 12–13.

27. Proceedings of the 4th International Symposium on Pertussis, held at NIH, 21 October 1963. This article is in the authors’ possession.

28. M. Haire, D. S. Dane, and G. Dick, “Reactions to Combined Vaccines Containing Killed *Bordetella pertussis*,” *The Medical Officer*, 1967, 117, 55–58, p. 13.

29. M. Kulenkampff, J. S. Schwartzman, and J. Wilson, “Neurological Complications of Pertussis Inoculation,” *Arch. Dis. Child.*, 1974, 49, 46–49.

damages are particularly tragic as they are iatrogenic and in most cases affect primarily completely healthy children.”³⁰

A chorus of criticism pounded the vaccine during the 1980s. By 1982 some physicians questioned whether the vaccine might be a generally unrecognized major cause of sudden infant and early childhood death and wondered if the risk of immunization might outweigh its potential benefits. In Britain parents were urged to seek compensation for children damaged by pertussis vaccine.³¹ In 1984, an FDA researcher reported that reactions from a single lot may vary from nil to severe and may include fever, shock, convulsions, persistent screaming, and encephalopathy. Neurological symptoms can occur early or be delayed for several days after injection.³² R. M. Barkin and colleagues in 1984 agreed that DPT has a high rate of adverse reactions, citing impressive incidence rates. As many as 93 percent of patients experience adverse reactions, including fever, acute behavioral change, and local reactions. Encephalopathy and permanent neurological sequelae occur in approximately 1 in every 310,000 immunizations. Other researchers agreed that the pertussis toxin caused cellular dysfunction in the central nervous system, with consequences ranging from irritability to coma.³³

In 1985 the U.S. IOM issued a report on the efficacy and safety of vaccines. About pertussis it concluded:

Low grade fever and local tenderness appear frequently after injection. Severe disturbing untoward reactions, including shock, convulsions, encephalopathy, and persistent high-pitched screaming, are rare complications. . . . The frequency of fatal reactions has been estimated to be one to two cases per ten million injections, and the frequency of serious neurological disorders such as encephalopathy to be one case per 110,000 injections with persistent neurological dysfunction after one year later.³⁴

30. O. T. S. Bajc, “Convulsions after Pertussis Vaccination,” *Schweiz. Med. Wschr.*, 1980, 110, 1965–71, p. 13.

31. W. C. Torch, “Diphtheria-Pertussis-Tetanus (DPT) Immunization: A Potential Cause of the Sudden Infant Death Syndrome (SIDS),” *Neurology*, 1982, 32, A169–A170; A. C. Wardlaw and R. Parton, *Medical Microbiology* (London: Academic Press, 1983), pp. 207–53.

32. M. Pittman, “The Concept of Pertussis as a Toxin-mediated Disease,” *Pediatr. Infect. Dis.*, 1984, 3, 467–86.

33. R. M. Barkin, J. S. Samuelson, and L. P. Gotlin, “DTP Reactions and Serologic Response with a Reduced Dose Schedule,” *J. Pediatr.*, 1984, 105, 189–94; L. E. Davis, D. G. Burstyn, and C. R. Manclark, “Pertussis Encephalopathy with a Normal Brain Biopsy and Elevated Lymphocytosis-Promoting Factor Antibodies,” *Pediatr. Infect. Dis.*, 1984, 3, 448–51.

34. U.S. Institute of Medicine, *New Vaccine Development: Establishing Priorities* (Washington, D.C.: National Academy Press, 1985), p. 14.

The report went on to state that the United States could save millions of dollars if acellular pertussis replaced whole-cell pertussis as the form of vaccination in children. Many other researchers echoed these conclusions.³⁵

Our own work in the late 1990s on adverse reactions following whole-cell DTP vaccination has been based on the Vaccine Adverse Events Reporting System (VAERS) database. VAERS is a passive epidemiological database that has been maintained by the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, since 1990. All vaccine-associated adverse reactions are to be reported to this database as mandated by U.S. law. We have analyzed the incidence of neurological adverse reactions reported to the VAERS database following whole-cell DTP administration since 1990 and have calculated the incidence rates of various types of adverse reactions to the vaccine based on the estimates of the CDC on the number of doses administered. Our studies were based on the administration of tens of millions of doses to American children and show that whole-cell DTP was statistically significantly linked with fevers, convulsions, and deaths beyond the childhood background rates.³⁶

ACELLULAR PERTUSSIS VACCINE

Because of the effectiveness of the vaccine program, pertussis had become only a minor infectious disease problem in the United States.

35. P. Ibsen, S. Moller, and I. Heron, "Lipopolysaccharides in a Traditional Pertussis Vaccine," *J. Biol. Stand.*, 1988, 16, 299-309; R. D. Sekura, Y. Zhang, R. Roberson, B. Acton, B. Trollfors, N. Tolson, J. Shiloach, D. Bryla, J. Muir-Nash, D. Koeller, R. Schmerrson, and J. B. Robbins, "Clinical, Metabolic, and Antibody Response of Adult Volunteers to an Investigational Vaccine Composed of Pertussis Toxin Inactivated by Hydrogen Peroxide," *J. Pediatr.*, 1988, 113, 806-13; J. H. Menkes, "Pertussis Vaccine Encephalopathy," *J. Am. Med. Assoc.*, 1990, 264, 2384; J. H. Menkes and M. Kinsbourne, "Workshop on Neurologic Complications of Pertussis and Pertussis Vaccination," *Neuropediatrics*, 1990, 21, 171-76.

36. D. A. Geier and M. R. Geier, "An Analysis of the Occurrence of Convulsions and Death after Childhood Vaccination," *Toxicol. Mech. Methods*, 2002, 12, 71-78. The purpose of this analysis was to review the VAERS database for attributed adverse events reported following the actual clinical immunization of American children with whole-cell DTP, acellular DTaP and DT vaccinations. This paper establishes that the chance association between serious adverse reactions, neurological adverse reactions and death cannot be accounted for by coincidence alone. The data clearly established that whole-cell DTP is far more reactogenic than acellular DTaP or DT vaccines; D. A. Geier and M. R. Geier, "Clinical Implications of Endotoxin Concentrations in Vaccines," *Ann. Pharmacother.*, 2002, 36, 776-80. The purpose of this study was to extend and expand previous studies to determine the endotoxin levels in commercially manufactured whole-cell DTP, acellular DTaP and DT vaccines and determine the clinical effects of each vaccine's use in children in the US. The results of the endotoxin assay showed that whole-cell DTP vaccines contained considerably more endotoxin than either acellular DTaP or DT vaccines. The VAERS

Therefore, the high level of toxicity of the whole-cell pertussis vaccine was rapidly becoming unacceptable to the general population. The scientific community's awareness of the dangers associated with whole-cell pertussis vaccine led to many different techniques and procedures to produce a less harmful variety. The first was developed by Parke-Davis and Company in the 1920s and consisted of just the bacterial cell wall and virtually no toxins.³⁷ Despite being a highly impure form of acellular vaccine, it was associated with markedly fewer adverse reactions than the whole-cell vaccine because it was free of the toxic components of pertussis bacterial cultures.

In 1937, Lederle Laboratories patented an acellular pertussis vaccine that used soluble pertussis toxin.³⁸ The cells were removed and the pertussis toxin was toxoided with formaldehyde. This vaccine was widely and successfully used in the United States in the 1940s and had some similarities to the acellular form widely used today. It was shown to be 94 percent protective in children with definite exposures to pertussis bacteria, which surpassed the protection offered by a whole-cell vaccine and roughly equates to the protection of the Japanese form of acellular vaccine currently used today. According to Lederle Laboratories head Dr. H. D. Piersma, the company actively marketed its 1937 acellular vaccine from 1944 to 1948, but ceased the marketing in 1948 when Lederle began production of Tri-Immunol DTP using a whole-cell pertussis component.³⁹ The whole-cell variety was used to avoid the need for laborious and expensive efficacy testing on an acellular version of the vaccine, which would have been required under new federal laws.

Another early acellular pertussis vaccine was the stromata-protective antigen (SPA) vaccine of Pillemer and colleagues in 1954. It was protective in the mouse potency assay and showed clinical efficacy

showed that statistically significantly more instances of fever, seizures, death, and permanent brain damage were associated with whole-cell DTP vaccine than acellular DTaP or DT vaccines.

37. W. A. Puckner, "Gonococcus Immunogen, Gonococcus Immunogen Combined, Streptococcus Immunogen Combined, Pertussis Immunogen Combined, and Pneumococcus Immunogen Combined Not Acceptable for New and Nonofficial Remedies," *J. Am. Med. Assoc.*, 1927, 984.

38. C. L. Joslin and T. A. Christensen, "Prophylaxis and Treatment of Whooping Cough with a Pertussis Antigen," *Am. J. Dis. Child.*, 1939, 1269-76.

39. H. D. Piersma (deposition), *Corbine vs. Lederle Laboratories* (American Cyanamid Co.), 21 March 1986; H. D. Piersma (deposition), *Nelson vs. American Cyanamid Company*, Case No. C84-235 A, U.S. District Court for the Northern District of Ohio, Eastern Division, 1985, 3-28. This deposition is in the authors' possession.

in British Medical Research Council trials in 1951 and 1956 but was never licensed for clinical use nor brought to market, primarily because of its higher cost of production and the cost of additional efficacy trials that would have been required to gain full licensure.⁴⁰

Since by the mid-1960s it was agreed that the mouse toxicity test was incapable of predicting and thus eliminating potential adverse reactions to whole-cell pertussis vaccine, the Eli Lilly Company decided to patent, license, and produce an acellular pertussis vaccine prepared from a trisodium phosphate extract of pertussis cells. This type of vaccine was described by Wehl and colleagues in their 1963 publication.⁴¹ This vaccine was widely sold from 1962 to 1977 under the name of Tri-Solgen as a component of their DTP Adsorbed vaccine. Lilly's vaccine cost more, but was well received by the medical community because it caused approximately 80 percent fewer reactions in children.⁴² In fact, Lilly's Tri-Solgen was so well received that between 1962 and 1967 the company captured 50 percent of the market, increasing to 65 percent of the market between 1972 and 1976.⁴³

Another commercially available acellular vaccine had been brought to market in 1960. This vaccine was studied in a number of field trials and reported to be both safer and more efficacious than whole-cell pertussis vaccine.⁴⁴ It was marketed for approximately two years in 1960 and 1961 by Merck Sharp and Dohme, but by 1963 the company had gone back to the use of its whole-cell vaccine, presumably because of cost pressures. However, in 1964 Merck withdrew all products with whole-cell pertussis vaccine from the market, citing a fear of lawsuits.⁴⁵ The rationale was that since bad reactions were

40. L. Pillemer, L. Blum, and I. H. Lepow, "Protective Antigen of *Haemophilus pertussis*," *Lancet*, 1954, 1, 1257-60; Medical Research Council, "Prevention of Whooping-cough"; "Vaccination against Whooping-cough."

41. C. Wehl, H. D. Riley, and J. H. Lapin, "Extracted Pertussis Antigen," *Am. J. Dis. Child.*, 1963, 106, 210-15.

42. Eli Lilly Laboratories, 1963 Symposium: Lilly Tri-Solgen Vaccine, 173. This article is in the authors' possession.

43. R. Meschke (letter), "Toxoid Consolidation Data," American Cyanamid, Sales Forecasting, 26 April 1977. This article is in the authors' possession.

44. R. Underwood (affidavit), "Whooping Cough Immunization Antigen," The United States Patent Office, Serial Number: 366,072, January 1960; H. M. Felton and W. F. Verwey, "The Epidemiological Evaluation of a Non-cellular Pertussis Antigen," *Pediatrics*, 1955, 16, 637-49.

45. M. V. Querry (letter), Merck Laboratories Internal Correspondence, 29 April 1966. This letter is in the authors' possession.

occurring with its whole-cell pertussis vaccine, Merck could be held legally liable if it had a safer, more effective product that it did not sell. Under a U.S. Army grant, a practical method for pertussis toxin purification was developed and published in 1964.⁴⁶ This method subsequently became the basis for the currently used Japanese-type acellular pertussis vaccines. Similar experimental vaccines were developed by Wyeth, Parke-Davis, and Lederle and were shown to be potent in the mouse potency assay, but these companies never marketed these products for general use. The main reason for failure to market these acellular vaccines was their cost. In the early 1960s, Millman and colleagues developed a soluble pertussis vaccine that was potent in the mouse potency assay, but was not tested in clinical trials to determine human efficacy due to cost considerations. In 1972, Merrell-National developed an acellular vaccine that passed the FDA potency and toxicity tests, but because the yield was low in the production process, the company decided not to seek FDA approval to commercially sell the safer vaccine.⁴⁷ This product was later purchased by Connaught Laboratories.

It is interesting that many of the manufacturers who produced experimental acellular vaccines but were unwilling to pay for the cost of their production have attempted to discredit Lilly's Tri-Solgen acellular vaccine. For instance, Connaught stated in 1979 there were serious doubts about Tri-Solgen's efficacy because it had never been subject to controlled field testing. In reality, Tri-Solgen underwent extensive trials in the 1960s. Additionally, during the many years that Tri-Solgen was the vaccine used by the majority of the millions of children in the United States, no significant increase in the rate of pertussis in the U.S. population was observed. However, Connaught claimed that in 1982, as a result of this lack of testing, the FDA had refused to grant a split cell license to Wyeth Laboratories, which had purchased Lilly's rights to the vaccine. In actuality, the Panel on Review of Bacterial Vaccines and Bacterial Toxoids reviewed Lilly's acellular Tri-Solgen in 1979, found it to be both safe and effective, and recommended that the product be placed in category I (the

46. Round Table Conference of Pertussis Immunization 1962, presented by I. Millman, L. F. Schuchardt, and A. Gray; Y. Juwajima, "Purification of Histamine Sensitizing Factor of *Bordetella pertussis*," U.S. Army Grant, 1964, 1-25. These articles are in the authors' possession.

47. L. Colio (deposition), *Terry Lynn Hall vs. Connaught*, 1986, 8-18. This deposition is in the authors' possession.

highest rating possible with regard to efficacy). It was a reformulation of the product by Wyeth after purchasing the patent from Lilly that caused the FDA to determine that Wyeth was attempting to produce a “misbranded” product and to reject its licensing.⁴⁸

During the 1960s and 1970s, pertussis manufacturing companies developed acellular pertussis vaccines, briefly used them, decided based on economic factors not to make them, and then were forced to withdraw from making any pertussis vaccine because of their knowledge of how to make a better vaccine and the legal ramifications of persisting in making and marketing an inferior product. Thus, the pertussis vaccine market contracted so much that out of the multitude of manufacturers making DPT in the 1940s and 1950s, only four were left by the 1970s. These were Wyeth, Lilly, Lederle, and Connaught. The only one of the four manufacturers actively making the safer and more effective acellular pertussis vaccine was Lilly. The rest deemed it too costly to have their experimental new acellular pertussis vaccines approved and produced on a massive scale. The result, as stated before, was that Lilly captured a lion’s share of the market with its much safer and more effective acellular product.

In 1975, however, Lilly stopped the manufacture of all of its biological products. Shortly thereafter, it offered its Tri-Solgen license to other manufacturers and Wyeth contracted to acquire the rights. When Wyeth reproduced Lilly’s Tri-Solgen in its laboratory, however, it immediately realized that the yield was only 20 percent. Faced with an unexpectedly large increase in the cost of production, Wyeth set about to change the formula to get more bang for the buck. By doing so, the company was able to get five times the yield that Lilly had achieved with its original formula. When Wyeth approached the government for approval of the reformulated Tri-Solgen, however, the government balked and threatened the company with “misbranding.”⁴⁹ Before the government would approve Wyeth’s reformulation, the manufacturer would have had to perform safety and efficacy trials. Wyeth contemplated doing a double-blind safety study comparing the reactogenicity of Lilly’s formulation of Tri-Solgen to its own

48. H. M. Meyer (letter), Director, Bureau of Biologicals, 9 March 1978 to A. Bernstein, Wyeth Laboratories. This letter is in the authors’ possession.

49. Rubin, “Bacterial Vaccine Studies,” Second Quarterly Report Wyeth Laboratories, 1977, 11; F. J. McCarthy (letter), Wyeth Laboratories Internal Correspondence, 14 February 1977 to A. Bernstein, Wyeth Laboratories; both in the authors’ possession; Meyer, letter to Director, Bureau of Biologicals.

whole-cell pertussis vaccine, but chose not to do so. The reason was best expressed by Wyeth scientist Dr. Howard Tint in his cryptic message on the proposed study, “A reply is needed to N. W. Fleischman (location 1800) who suggests that possibly we might not want to see the basic study carried out at all at this time.”⁵⁰ Dr. Tint knew that a study would show Wyeth’s whole-cell pertussis vaccine was far more reactive than Lilly’s acellular product, which would open the door to potential legal liability against Wyeth for its past failure to market its acellular pertussis vaccine.

After years of embattled discussion within Wyeth, the decision was eventually made to produce only whole-cell pertussis vaccine, but by 1984 Wyeth had completely dropped out of the pertussis vaccine market. The result was that only two manufacturers, Lederle and Connaught, remained, each of which was only producing whole-cell pertussis vaccine in the United States.

PERTUSSIS VACCINATION IN OTHER COUNTRIES

Incidents with pertussis vaccination in Japan, England, and Sweden began to have profound effects on American perceptions of the safety and efficacy of whole-cell pertussis vaccination. In 1976, two babies in Japan died as a result of DPT vaccinations. The Japanese government, fed up with the continued use of the reactive whole-cell pertussis vaccine given to it by the United States after World War II, sent one of its scientists, Dr. Yugi Sato, to the National Institutes of Health in the United States to study purification of the product. After less than one year of investigation—using American technology developed in the 1950s and 1960s—Sato developed an acellular pertussis product. The production lots of Japanese acellular pertussis vaccine contain less than one-twentieth of the endotoxin of a comparable whole-cell pertussis vaccine and less than 4 percent of the amount of active pertussis toxin. Yet Sato and his colleagues reported near 100 percent vaccine efficacy.⁵¹ The Japanese conducted trials of Sato’s acellular vaccine between 1978 and 1981. As a result of the positive findings of the trials, Japan made the decision on 31 October 1981 to use only acellular pertussis vaccine.

50. H. Tint (letter), Wyeth Laboratories Internal Correspondence, 27 June 1977, p. 19–20. This letter is in the authors’ possession.

51. Y. Sato, H. Sato, K. Izumiya, J. L. Cowell, and C. R. Manclark, “Role of Antibody to Filamentous Hemagglutinin and to Leukocytosis Promoting Factor-Hemagglutinin in

In response to the controversy surrounding whole-cell pertussis vaccination in the United Kingdom, the National Childhood Encephalopathy Study (NCES) was begun in 1976 to determine whether whole-cell pertussis vaccine caused brain damage in children and, if it did, to establish how often such damage occurred. This was a prospective case-control study, which reported on the first 1,000 cases for the three years ending 30 June 1979.⁵² A case was defined as an acute neurological illness in a two- to thirty-six-month-old child who required hospitalization. Permanent brain damage was defined as a case with residual effects after one year. For previously normal children, the estimated risk of permanent neurological illness attributed to immunization with DTP vaccine was one in 310,000 immunizations.⁵³ The conclusions of the National Childhood Encephalopathy Study were as follows:

1. Most cases of acute and potentially damaging neurological illness in early childhood are attributable to causes other than immunization.
2. Neurological illnesses occur more frequently within seventy-two hours after DTP vaccination than would be expected by chance.
3. Most, but not all, children who manifest neurological illness make a complete recovery.
4. Considering possible alternative explanations of the clinical findings in cases associated with the DTP vaccine and considering the fact that similar cases occur after DT vaccine but at a much lower rate, it seems likely that permanent damage as a result of pertussis immunization is a real but rare event.⁵⁴

An evaluation of the results of the National Childhood Encephalopathy Study by the United Kingdom's Committee on Safety of Medicines and the Joint Committee on Vaccination and Immunization noted that no causal relationship had been established between

Immunity to Pertussis," *Semin. Infect. Dis.*, 1982, 4, 380-85; Y. Sato, M. Kimura, and H. Fukumi, "Development of a pertussis component vaccine in Japan," *Lancet*, 1984, 1, 122-26.

52. R. Alderslade, M. H. Bellman, N. S. B. Rawson, E. M. Ross, and D. L. Miller, *Whooping Cough* (London: H.M. Stationary Office, 1981), pp. 79-169.

53. It should be noted that in the United States most children get five doses. Thus, based on these figures, the best estimate is that 1 in 60,000 American children has suffered major permanent brain damage from the whole-cell vaccine. In addition to this rare rate of major brain damage, there is the possibility that the highly neurotoxic whole-cell pertussis vaccine may cause minor brain damage in a much higher percentage of vaccine recipients. This damage might manifest itself in loss of intelligence quotient points, reading problems, language difficulties, or autism. Since these types of brain damage show up years after vaccination, we may never know who was truly damaged by whole-cell pertussis vaccination.

54. Alderslade et al., *Whooping Cough*, pp. 21-22.

DTP immunization and serious neurological illness, but there was strong evidence that a link might exist for some children. Advisory panels in the United Kingdom and the United States reaffirmed their respective positions that whole-cell pertussis vaccine effectively protects against pertussis, a disease that also causes severe brain damage, and that the advantages of vaccination in preventing pertussis outweighed the risks associated with its use.⁵⁵

In the 1970s, however, Sweden banned the use of whole-cell pertussis vaccine. After several studies were published there, the government concluded that the benefit did not outweigh the risk. The chief Swedish authority in this finding was Dr. Wolfgang Ehrengut. He pointed out in 1985 that there had not been a single death from pertussis, even without vaccination, since 1970. He also stated that a causal connection between whole-cell DPT and encephalopathies had clearly been shown. Therefore, he felt that parents had a right to know the pros and cons of pertussis vaccination for their children and that there should be generalized immunization against pertussis with a less dangerous vaccine.⁵⁶

Because of its stance on vaccination, Sweden became a good place to test the safety and efficacy of the Japanese acellular vaccine in human populations against the incidence and associated risks of the actual infectious disease pertussis. Unfortunately, when the test procedures were formulated, no whole-cell pertussis vaccine could be administered in Sweden because it had been banned. An ideal study would have had two control groups, one receiving whole-cell DTP vaccine and one receiving acellular DTaP vaccine so that comparative figures could be analyzed. Instead, the researchers assumed that the whole-cell pertussis vaccine was approximately 80 percent effective at preventing infection by pertussis in human populations. When the study figures of acellular efficacy came in at 55 percent and 69 percent, it initially looked like the Japanese acellular pertussis vaccine was not as effective as the whole-cell pertussis vaccination was originally believed to be. It was only afterward that scientists went back to question the assumed 80 percent efficacy rate of whole-cell DTP vaccine. As it turned out, according to some studies whole-cell pertussis vaccine is only 45–48 percent effective in preventing pertussis

55. Immunization Practices Advisory Committee, *Mortal. Morbid. Weekly Rep.*, 1981, 30, 392–407.

56. W. Ehrengut (letter), 19 November 1985. This letter is in the authors' possession.

infection in humans.⁵⁷ Another problem the researchers encountered in determining efficacy was how to define the disease pertussis. Was culture confirmation necessary? An extended cough for several months with the characteristic “whoop”? For example, a person might have a culture of confirmed pertussis but only have a mild cough for a week. Did that mean the person had pertussis or did that mean the vaccine had been effective? After the original publication, the Swedish scientists did a reanalysis. They determined that Japanese acellular pertussis vaccines were more effective than whole-cell pertussis vaccines, even though only two doses of acellular pertussis vaccine were required, whereas the whole-cell pertussis vaccine is usually given in a five-dose schedule.⁵⁸

THE AMERICAN RESPONSE TO WHOLE-CELL PERTUSSIS VACCINATION

The decline in the incidence of whooping cough by the late 1970s led the American public to become concerned that the vaccine might pose greater risks than the disease. The concern was generated by emotionally effective presentations in newspapers and television that questioned the need for continued vaccination in the virtual absence of the disease, especially considering the potentially harmful side effects associated with vaccination. Additionally, it was argued, modern medical treatments including antibiotics could easily treat those infected with the disease.⁵⁹ The American public became even more aware of the potential for difficulties resulting from whole-cell pertussis vaccination in 1978 when all public health clinics using federally purchased vaccines were required by the FDA to have parents sign an “important information statement” about the risks of immunization before their children could be vaccinated.⁶⁰ It was deemed necessary to obtain informed consent for this required procedure because of the overwhelming data that indicated whole-cell pertussis vaccine could result in severe adverse reactions. Also in that year the Centers for Disease Control created the Monitoring System for Illness Follow-

57. S. A. Halperin, R. Bortolussi, D. MacLean, and N. Chisholm, “Persistence of Pertussis in an Immunized Population: Results of the Nova Scotia Enhanced Pertussis Surveillance Program,” *J. Pediatr.*, 1989, 115, 686–93.

58. L. Seachrist, “New Pertussis Vaccines Safer, More Effective,” *Science*, 1995, 148, 54.

59. W. G. Rothstein, *Readings in American Healthcare: Current Issues in a Socio-Historical Perspective* (Madison: The University of Wisconsin Press, 1995), pp. 111–28.

60. Coulter and Fisher, *A Shot in the Dark*.

ing Immunization (MSIFI) as a direct result of the difficulties encountered in the United States with the swine flu vaccine.

Growing concern prompted more study on the reactogenicity of whole-cell pertussis vaccine. Clinical studies of the more common adverse reactions were compiled by Barkin and Pichero in 1979 and by Hopkins in 1979.⁶¹ In a prospective study reported by Cody and colleagues in 1981, reaction rates were recorded after the injection of DTP and DT vaccines to determine what influence the whole-cell pertussis component had on adverse reaction rates. The reaction DTP/DT rates were as follows: "local redness, 37.4/7.6 percent; local swelling, 40.7/7.6 percent; pain, 50.9/9.9 percent; fever, 31.5/14.9 percent; drowsiness, 31.5/14.9 percent; fretfulness, 53.4/22.6 percent; vomiting, 6.2/2.6 percent; anorexia, 20.9/7.0 percent and persistent crying, 3.1/0.7 percent. Nine of 15,752 DTP immunizations resulted in convulsions, and nine other children had hypotonic hyporesponsive episodes."⁶²

A landmark event in the evolution of vaccine toxicity awareness occurred in 1979 when the CDC held meetings to discuss the relationship between sudden infant death syndrome (SIDS) and pertussis vaccine after a lot of DPT administered in Tennessee was believed to be responsible for several deaths. Four infants, all aged two to three months, died within twenty-four hours of receiving Wyeth lot 64201. There were 96,105 doses of this lot given in Tennessee before the state withdrew the lot from use on 11 March 1979. An article in *Morbidity and Mortality Weekly Report* later showed that the DPT vaccine was statistically significantly linked to these deaths.⁶³ As news of the tragedy spread, Dr. Ted Cannon, the second-in-command of the FDA in charge of vaccines, ordered the recall of the entire lot from the shelves in several states. The FDA head of vaccines, Dr. John Petricciani, was away at the time. Upon returning, however, he issued a memo stating that the potential harmful lots of pertussis vaccine had to be put back on the shelf for use, and he apologized

61. R. M. Barkin and M. E. Pichichero, "Diphtheria-Pertussis-Tetanus Vaccine: Reactogenicity of Commercial Products," *Pediatrics*, 1979, 63, 256-60; R.S. Hopkins, *International Symposium on Pertussis* (Washington, D.C.: U.S. Government Printing Office, 1979).

62. C. L. Cody, L. J. Baraff, J. D. Cherry, S. M. Marcy, and C. R. Manclark, "Nature and Rates of Adverse Reactions Associated with DTP and DT Immunizations in Infants and Children," *Pediatrics*, 1981, 68, 650-60.

63. R. Hutchinson, "DTP Vaccination and SIDS—Tennessee," *Mortal. Morbid. Weekly Rept.*, 1979, 131-32.

to the drug companies for the actions taken by the FDA, assuring them it would never happen again.⁶⁴ Petricciani's apology came after strong pressure was applied by the vaccine manufacturers, who were unwilling to lose revenue due to an informal recall of their vaccine. They took measures of their own to ensure against future recalls. After the Tennessee incident, pertussis manufacturers arranged that entire lots would never again be sent to single areas of the country. Specifically, a memo from Wyeth Laboratories stated that since the SIDS episode, there had been only a limited number of vials of each lot of DTP shipped to municipal clinics, not exceeding more than 2,500 vials.⁶⁵ This small lot plan meant that no one region of the country would have enough adverse reactions to a single lot of whole-cell pertussis vaccine to alert the clinicians in that region to the fact that they were using a highly reactogenic lot.

The first legal difficulties over whole-cell pertussis vaccine came almost two decades before the Tennessee deaths. They were generated by the Parke-Davis Quadrigen vaccine in the 1960s. In this vaccine, a whole-cell DTP was combined with a Salk killed polio vaccine component. It was licensed for use in 1959, and immediately adverse reactions began to be reported. The result was several successful lawsuits in which it was alleged that the preservative used in the pertussis component was extremely reactogenic. Quadrigen was subsequently withdrawn from the market; however, the reports of severe adverse reactions to whole-cell DTP continued.⁶⁶

The next major suit came in 1981 from Ken Pederson of an Idaho law firm that sued and won a large judgment from Lederle Laboratories on the grounds that their whole-cell pertussis vaccine was a defective product. This verdict was appealed and upheld all the way to the U.S. Supreme Court, which refused to hear the case. Another landmark case was tried by Ted Worshofsky and Victor Harding in Wichita, Kansas. These successful cases had significant implications for the future of whole-cell pertussis vaccination use in that they were brought on the grounds that the product was defective and that the vaccine manufacturers had known for many years how

64. G. M. Irwin (letter), Wyeth Laboratories Internal Correspondence, 25 January 1983 to M. Z. Bierly. This letter is in the authors' possession.

65. A. Bernstein (letter), Wyeth Laboratories Internal Correspondence, 27 August 1979 to L. Hewlett. This letter is in the authors' possession.

66. Coulter and Fisher, *DPT: A Shot in the Dark*.

to produce a more effective and far safer pertussis vaccine, but had failed to bring these products to market due to financial considerations.⁶⁷

In 1982, the television program “DPT: Vaccine Roulette” was first broadcast by NBC affiliate WRC-TV in Washington, D.C., and was widely publicized. The program depicted children with severe injuries reported to be associated with whole-cell pertussis vaccine, along with attorneys Alan McDowell and Toni Colantoni. This television program raised parents’ awareness so much that soon McDowell and Colantoni had literally hundreds of lawsuits to file against the vaccine manufacturers. Michael Hugo, an attorney from Massachusetts, contributed to the effort by compiling a library of information for use by other plaintiff attorneys concerning whole-cell DPT and its manufacture. At first these attorneys had great difficulties in finding expert witnesses not attached to the vaccine manufacturers or the U.S. government, yet who were knowledgeable enough and willing to testify in these cases. The first major expert witness to testify against the vaccine manufacturers was Kevin Geraghty, M.D., a California pediatrician. In attempt to prevent Geraghty from testifying, he and his family were harassed by the vaccine manufactures to such an extent that he filed a suit against them. It is at this point that Mark Geier, M.D., Ph.D., became involved in the pertussis cases. A Maryland geneticist who had previously studied vaccine problems at the NIH, Geier was approached by the law firm of McDowell and Colantoni, who eventually convinced him that he also needed to testify against the vaccine manufacturers. These two experts were soon joined by Arthur C. Zahalsky, Ph.D., an immunologist from Southern Illinois University. Once the ice was broken, other expert witnesses came forward to testify against the vaccine manufacturers, making it virtually impossible for the manufacturers to stop everyone from testifying. By 1985, 219 lawsuits had been filed in U.S. courts alleging harm to children from whole-cell pertussis vaccination.⁶⁸

In addition to the dramatic legal actions taken against whole-cell pertussis vaccine producers, American parents began to band together. The first and most powerful group was—and still is—the advocacy group Dissatisfied Parents Together (DPT), which was formed in

67. U.S. Institute of Medicine, *Adverse Events*.

68. *Ibid.*

1982 by Barbara Loe Fisher. Its members called for research toward a safer pertussis vaccine and mandatory reporting of all adverse reactions to vaccines. Additionally, in 1985 Fisher and Dr. Harris Coulter published the book *A Shot in the Dark*, which educated parents about the potentially harmful effects of childhood immunizations. Within a year of the formation of DPT, the group's messages became so strong that the American Academy of Pediatrics was forced to conduct more than eight months of hearings to discuss recommendations for a federal compensation program for children with vaccine-related illnesses and injuries.⁶⁹ The result of these discussions, along with the large-scale civil litigation against the manufacturers, helped spur the introduction of the National Compensation Act (S-2117) in 1983 by Senators Paula Hawkins and Orrin Hatch. The goal of this act was to set limits on liability for vaccine-related disabilities. In order to encourage its passage, a vaccine manufacturer agreed to settle one of the cases against it for a total of 26 million dollars.⁷⁰ The manufacturer then cited this large settlement as an example of why it needed protection against litigation if it was going to continue to manufacture vaccines.

By the mid-1980s it seemed that litigation and political action groups were being more effective in bringing about change in vaccine policy than the government agencies regulating the vaccines. But in 1986, Public Law 99-660, the National Vaccine Injury Act, was passed by the United States Congress. The law called for the establishment of the National Vaccine Program (NVP) to achieve optimal prevention of human infectious diseases through immunization and to achieve optimal prevention against adverse reactions to vaccines. Additionally, the law called for the establishment of the National Vaccine Advisory Committee (NVAC) to advise the director of the NVP, the National Vaccine Injury Compensation Program (VICP) to evaluate claims of injury from vaccines and to provide compensation where justified, and the Advisory Commission on Childhood Vaccines (ACCV) to advise the Secretary of the Department of Health and Human Services and the VICP on vaccine policy. This law also mandated a scientific review of possible adverse effects of whole-cell

69. Coulter and Fisher, *A Shot in the Dark*.

70. J. P. Koplan and A. H. Hinman, "Decision Analysis, Public Policy, and Pertussis: Are They Compatible?" *Med. Decision Making*, 1987, 7, 72-73.

pertussis vaccine by the Institute of Medicine of the National Academy of Sciences.⁷¹

The National Vaccine Compensation Act requires that persons damaged by a vaccine seek compensation under the VICP before filing a civil claim against the vaccine manufacturers. Although this act did benefit victims by providing them with another mechanism by which to receive compensation, it also protected the vaccine manufacturers from most civil litigation and, in fact, muted litigation then pending against the manufacturers, which helped to remove the pressure on them to move from whole-cell pertussis to acellular pertussis vaccination. Congress foresaw that the act might slow down progress in converting from a whole-cell to an acellular pertussis vaccine, so to help ameliorate this problem, it also appropriated funds and charged the IOM to hold hearings and make recommendations for vaccine improvement.⁷²

But additional difficulty with the whole-cell pertussis vaccines used in the United States erupted again in 1989 when the FDA recalled Connaught Laboratories DPT lot 8M91039 because of possible contamination of the vaccine with equine influenza vaccine. The potential contamination occurred because Connaught was using the same equipment on successive days to make and fill veterinary products that it used for making and filling human vaccines. The company agreed that some children might well have been injected with the vaccine that was intended solely for use in horses, but it also felt it was unlikely that the children were damaged by the veterinary-grade product.⁷³

THE VACCINE COMPENSATION ACT

The National Vaccine Program established under Public Law 99-660 first began to operate in 1987 under the directorship of the assistant secretary of health of the Department of Health and Human Services. The first meeting of its advisory committee was not held until June 1988, however, and the actual operation of the injury compensation program, the VICP, did not begin until 1989. It was administered by

71. U.S. Public Law 99-660.

72. *Ibid.*

73. M. R. Geier (letter), Medical/Legal Consultant, 28 August 1989 sent to Dr. M. C. Hardegee, Director, FDA Office of Biological Research. This letter is in the authors' possession.

the secretary of the Department of Health and Human Services (HHS) through the staff of the Health Resources and Services Administration. By the end of its first year of operation, the VICP had received 201 petitions for compensation, of which 165 were related to DPT vaccine.⁷⁴

The act was originally passed to provide rapid and generous justice to those American citizens who were damaged by a vaccine that they were taking for the public good. It was initially funded by the U.S. Congress for \$600 million and was to be funded in the future by a small tax to be charged on each vaccine dose given. Implementation of the act was to be no-fault and nonlitigious, and in all claims, HHS was to be the respondent. A person or his or her guardian who believed that a vaccine had caused damage could file a petition for compensation. The act also required that HHS advertise and make known that anyone who believed they were damaged by a vaccine prior to the passage of the Act could petition for damages, no matter how long ago the adverse reaction occurred. HHS was to have the petition read by a neutral expert physician, who was to recommend for or against paying the claim. If the decision was unfavorable, the petitioners could request a hearing on the matter before a special master working for the U.S. Court of Claims. Since the act's inception, the chief special master has been Gary Golkiewicz. Petitioners could be represented by counsel and could bring experts to testify on their behalf. Petitioners' attorneys and experts were to be paid by the VCA, win or lose, so long as the action was brought in good faith. When Congress passed the act, it included a Vaccine Compensation Table and Aids of Interpretation to the Table that described in detail the timeframe and symptoms expected in patients damaged by a vaccine. If a petitioner could demonstrate that his or her case fit the table, he or she would receive an award for damages unless HHS could prove an alternative cause. If a petitioner's case did not fit the table, the burden of proof shifted to the petitioner to prove that the vaccine had caused the damage claimed.⁷⁵

Despite this congressional mandate, for approximately one year after the passage of the VCA, HHS refused to defend the cases, maintaining that it lacked the staff to adequately act as respondent.

74. U.S. Institute of Medicine, *Adverse Events*.

75. U.S. Public Law 99-660.

Since the act stated that anyone who filed a claim would have that claim adjudicated within six months or they would win by default, most of the early claims were won by default or through virtually unopposed hearings. Then things began to get more difficult for the petitioners based upon the experience of Dr. Geier, who made close to 100 appearances as an expert witness before the VCA. HHS asked for and finally got permission to have U.S. Justice Department lawyers defend the cases on its behalf. Then HHS, as the respondent, claimed the right to begin to change the rules of the act by administrative means. Among the changes made, one involved the dropping of the six-month time guarantee of adjudication. As a result, some cases have dragged on for nearly a decade, despite the fact that Congress's original intent was to grant rapid justice to vaccine victims. During these years, HHS began to shrink the table described in the original act. As the table got smaller, more and more of the burden of proof was shifted from the respondent to the petitioners. The VCA also started to adjust the amount of legal fees paid to the petitioners' lawyers and experts, making it more and more difficult for petitioners to find qualified help in bringing cases under the VCA. Since it often took years for cases to be heard, it also took years for lawyers and experts to be paid, even if the cases were won and even after the judgments were entered.

In a final assault on the act, HHS did not use neutral medical reviewers, but rather experts trained in how to help defend cases. Despite the fact that Congress had thought most cases would be settled administratively, HHS basically chose to oppose payment in virtually all cases, thus making bringing petitions under the VCA a litigious process. This process was not a predictable one, either, because the special masters of the VCA were not bound by their own previous rulings. Thus, no precedents were ever set, and it was difficult to know in advance which cases were most likely to be deemed compensable by looking at previous rulings in similar cases. The usual position of HHS's experts was that whatever happened following a vaccine was not caused by the vaccine, but rather was only coincidentally associated in time with it. Their argument was that almost all children receive multiple vaccines, mostly in the first year of life. Many of these same children are first discovered to have neurological conditions in that first year of life. Therefore, it follows as a matter of coincidence that many children will be discovered to have a neuro-

logical problem shortly following vaccination. Most of the petitioners' experts, on the other hand, maintained that if an apparently neurologically intact child has his or her first neurologically significant symptom closely following a vaccine, and if no provable alternative cause could be found despite a good medical analysis, then more likely than not the vaccine caused the neurological problem.

The VCA has resulted in a dramatic reduction in the number of civil court cases filed against vaccine manufacturers. Unfortunately, it has not resulted in rapid, generous, and nonlitigious justice. The bureaucracy of the Health and Human Services has defeated the original intent of Congress in passing the act.

THE COUNTERRESPONSE TO DIFFICULTIES
WITH WHOLE-CELL PERTUSSIS VACCINE

Because vaccine manufacturing companies are among the most interested in studying vaccines, they often provide large sums of money to researchers willing to do so. Such researchers, because they are well-funded and clinically knowledgeable, often develop reputations for their expertise, and thus they are often invited to serve on committees that make recommendations about vaccine policy. Such a system often results in conflicts of interest because researchers whose livelihoods strongly depend on financial ties to vaccine manufacturers are often the ones making the policy decisions that impact the financial future of the vaccines. In the pertussis vaccine field, one of the most egregious examples of such a conflict of interest is Dr. James Cherry, a professor at the University of California, Los Angeles, who spearheaded an attempt to change the philosophy of the scientific community regarding the whole-cell pertussis vaccine.

Cherry was and continues to be one of the most prolific writers on the topic of pertussis and pertussis vaccines. His published articles number in the hundreds and are cited at least once in virtually every article written by an author in this field. He also has written chapters on infectious disease in the leading textbooks, such as *Nelson's Textbook of Pediatrics*.⁷⁶ In a 1979 lecture at a symposium sponsored by Connaught, Cherry stated that all physicians are aware that whole-cell pertussis vaccine occasionally produces severe reactions and that these

76. J. D. Cherry, "Encephalitis," in R. E. Behrman and V. C. Vaughn, eds., *Nelson's Textbook of Pediatrics*, 12th ed. (Philadelphia: W. B. Saunders Company, 1983) pp. 626-31.

may be associated with permanent sequellae or even death.⁷⁷ But during the 1980s Cherry became a regular consultant and expert witness on the side of the pharmaceutical industry, consistently testifying and publishing that there was no proof that whole-cell DPT caused permanent brain damage.⁷⁸ In 1988, Cherry headed a select committee purportedly appointed to review the data on pertussis vaccine and its ability to cause permanent brain damage and to publish findings which would become the official position of the American Academy of Pediatrics. The academy's own records not only showed that it had accepted large gifts from the various whole-cell pertussis manufacturers, but also that the letters of appointment to the members of the select committee told them that they were to find that the vaccine did not cause permanent brain damage.⁷⁹ Not surprisingly, the committee did an extensive review of the literature on adverse reactions to pertussis vaccine, the vast majority of which showed a link between the vaccine and permanent damage in children, but for one reason or another it found fault with all of the old studies establishing causation. In 1992, the American Academy of Neurology published a similar position statement.⁸⁰ The announcement of the Academy of Pediatrics position was followed shortly thereafter by a paper reporting on a vote taken by the Pediatric Neurology Society: The majority of its members voted in support of the proposition that pertussis vaccine was not proven to cause permanent brain damage. The information in the paper was based on the vote and reflected little scientific research; only twenty-one scientific references were cited. However, Dr. John Menkes, the author of a leading pediatric neurology textbook and one of the very few pediatric neurologists

77. J. D. Cherry and E. A. Mortimer, "An Old Bacterial Vaccine with New Problems: Pertussis Vaccine—Recent Experiences," *Pediatric Immunization Today*, Connaught Laboratories Symposium, 1979, 12–15. This article is in the authors' possession.

78. J. D. Cherry (deposition), *Bobby Hardaway and Wife, Shirley Hardaway, etc., vs. The Metropolitan Government of Nashville, etc., et al.*, U.S. Federal Court, Middle District of Tennessee, Nashville Division, Civil Action Number: 3-87-0355, 24 June 1988, 44–46. This deposition is in the authors' possession.

79. J. D. Lockhart (letter), Director, Department of Maternal, Child and Adolescent Health, American Academy of Pediatrics, 21 December 1984 to D. T. Karzon, Department of Pediatrics, Vanderbilt University School of Medicine. This letter is in the authors' possession.

80. J. D. Cherry, P. A. Brunell, G. S. Golden, and D. T. Karzon, "Report of the Task Force on Pertussis and Pertussis Immunization—1988," *Pediatrics*, 1988, 81, 939–77; American Academy of Neurology, "Assessment: DTP Vaccination," *Neurology*, 1992, 42, 471–72.

who actually knew much about pertussis vaccine problems, was a vocal dissident in the voting.⁸¹

Cherry's point of view on pertussis vaccination culminated in a 1990 *Journal of the American Medical Association* editorial entitled, "Pertussis Vaccine Encephalopathy: It Is Time to Recognize It as the Myth That It Is."⁸² In order to have an article published in the *Journal of the American Medical Association*, an author is first required to identify any affiliations and financial involvements that might be considered a conflict of interest. Cherry attested that he had no financial arrangement with the DPT manufacturers. However, a New England television show, after careful research, revealed that his statements were misleading.⁸³ After a number of conflicting statements about what Cherry knew he was signing, the *Journal of the American Medical Association* published a retraction that disclosed his ties to the drug manufacturers.⁸⁴ What the retraction did not report was the extent of those ties. Since 1985, Cherry has received more than half a million dollars in gifts from Lederle alone. If one also considers the money he received in research grants from Lederle—money which was paid to the University of California, Los Angeles, but was used to support his department—Lederle's payments to Cherry since 1985 totaled more than 1.5 million dollars. Finally, if one includes his fees for serving as an expert witness for Lederle, Connaught, and Wyeth in more than eighty-five different cases involving adverse DPT vaccination reactions, Cherry's interest in the drug manufacturers approaches two million dollars.⁸⁵ The Congressional Committee on Government Operations investigating Scientific Misconduct and Conflicts of Interest cited Cherry for his failure to be forthright.⁸⁶

81. Pediatric Neurology Society, "Pertussis Immunization and the Central Nervous System," *Ann. Neurol.*, 1991, 29, 458–60.

82. J. D. Cherry, "Pertussis Vaccine Encephalopathy: It Is Time to Recognize It as the Myth That It Is?" *J. Am. Med. Assoc.*, 1990, 263, 1679–80.

83. J. D. Cherry (interview), Channel 7 News, WHDH-TV, Boston, Mass., March 1990. This videotape is in the authors' possession.

84. J. Scott, "Researcher to Clarify Ties to Drug Company," *Los Angeles Times*, 24 March 1990, p. B3; J. D. Cherry (deposition), *Hardaway vs. Nashville*. The deposition is in the authors' possession.

85. J. D. Cherry (interview), Channel 7 News.

86. The U.S. House of Representatives, *Are Scientific Misconduct and Conflicts of Interest Hazardous to our Health?* (Washington, D.C.: U.S. Government Printing Office, 1990), p. 65.

Following Cherry's 1990 *Journal of the American Medical Association* article, a similar article titled "A Pertussis Vaccine Myth Dies" was published in 1990 by Vincent Fulginiti in *American Journal of the Diseases of Childhood*. That same year, "Pertussis Vaccine and Injury to the Brain" was published by Gerald Golden in *The Journal of Pediatrics*. In this article, Golden stated that while there was clearly an increased risk of convulsions after whole-cell DTP immunization, there is no evidence that this produces brain injury or leads to epilepsy.⁸⁷

In addition to these new experts stating their position that whole-cell pertussis did not have the ability to produce adverse reactions, there were two landmark decisions in British and Canadian courts. In both the Loveday judgment in Great Britain's High Court of Justice, Queen's Bench Division, and the Rothwell judgment in the Supreme Court of Ontario, Canada, justices ruled that there was insufficient evidence to demonstrate that pertussis vaccine could cause permanent brain damage in children.⁸⁸ The British case set a precedent throughout the entire Commonwealth, becoming known as a "test case." This meant that all future lawsuits claiming pertussis vaccine adverse reactions among children in the British Commonwealth were prohibited. There are several interesting things to note about the Loveday decision. The first is that England had long been compensating its citizens who had been damaged by pertussis vaccine through a national vaccine compensation program. It is also interesting to note that many scientists and experts employed by Burroughs-Wellcome, the British producer of whole-cell pertussis vaccine, were invited to testify in Loveday, but not one member of the British-sponsored NCES study on pertussis vaccination reactions was allowed to testify. NCES had concluded in 1983 that whole-cell pertussis vaccine caused permanent brain damage in normal children. Yet the NCES researchers were not called to testify, even though they had expertise and for the fact that they had no conflicts of interest regarding the production of whole-cell pertussis vaccine.⁸⁹ In the Rothwell

87. G. S. Golden, "Pertussis Vaccine and Injury to the Brain," *J. Pediatr.*, 1990, 116, 854-61.

88. S. Stuart-Smith, judgment in *Loveday vs. Renton and Wellcome*, Royal Courts of Justice, London, 30 March 1988; J. Osler, judgment in *Rothwell vs. Raes, Hall, and Connaught Laboratories*, Supreme Court of Ontario, 18 November 1988. These judgments are in the authors' possession.

89. *Loveday vs. Renton*.

case in Canada, the verdict was the same—insufficient evidence to demonstrate direct neurological damage by the vaccine.⁹⁰

THE TRUTH FINALLY COMES TO LIGHT

Despite the appearance in 1990 that whole-cell pertussis vaccine had been completely exonerated, a decade later it was abandoned by American physicians. The undercurrent of criticism against it would triumph in the 1990s. In the 1985 IOM report of the U.S. National Academy of Sciences, after an extensive review of the problem of adverse reactions to pertussis vaccine, the IOM gave the highest possible priority to switching from whole-cell pertussis vaccine to acellular pertussis vaccine in order to prevent monetary loss and personal suffering. The panel estimated that there were approximately 18 million doses of whole-cell DPT vaccine given each year. Those injections caused 7.2 million cases of minor reactions, 10,300 seizures, 164 cases of encephalitis, and 60 cases of chronic disability, with costs running into the millions. The panel also estimated that the whole-cell DPT caused two to four deaths per year.⁹¹

This report, however, was widely ignored and put on a back shelf. When Geier appeared before another IOM committee in 1990 and presented the data from the 1985 report, members asked where the data were from. They were surprised to learn that the data came from their own archives. After extensive hearings, this 1990 IOM committee concluded that the evidence was sufficient for them to state that whole-cell pertussis vaccine caused acute encephalopathy. They were unable to conclude satisfactorily whether whole-cell pertussis vaccine caused permanent brain damage.⁹²

In 1993, the IOM met a third time to consider the new data on pertussis vaccination safety. This time they concluded that the data were compatible with a finding that whole-cell DTP causes permanent brain damage.⁹³ Following the publication of the 1994 IOM report, the U.S. Department of Health and Human Services published a similar conclusion as its official position in the *Federal Register*.⁹⁴ The American Academy of Pediatrics also notified its membership

90. *Rothwell vs. Raes*.

91. U.S. Institute of Medicine, *Vaccine Development*.

92. U.S. Institute of Medicine, *Adverse Events*.

93. U.S. Institute of Medicine, *DPT Vaccine and Chronic Nervous System Dysfunction: A New Analysis* (Washington, D.C.: National Academy Press, 1994).

94. "IOM Analysis of 10 Year Follow-up Study of NCES," *Fed. Reg.*, 23 March 1994, p. 59.

of this position.⁹⁵ These changes in position began to occur for a number of reasons. First, in 1993 the British NCES group published a follow-up study, ten years after its original report, that persisted in arguing that whole-cell DTP vaccine caused neurological damage and that it was permanent.⁹⁶ Second, a group of judges working for the VCA had awarded large amounts of money to petitioners whom the judges believed had proven permanent neurological damage after whole-cell pertussis vaccination. Third, pressure from civil litigation again began to be a threat to the vaccine manufacturers. Fourth, and most important, the vaccine manufacturers who made whole-cell pertussis vaccine became aware that several new companies were gearing up for licensure and production of acellular pertussis vaccines in the United States. They had to make acellular pertussis vaccine if they wanted to protect their market position.⁹⁷

As a result of the publication of the 1993 follow-up NCES study and the 1994 IOM report, we were able to analyze the frequency of encephalopathies associated with whole-cell DTP vaccination. We showed that whole-cell DTP vaccination was more likely than not responsible for causing encephalopathic reactions with a reasonable degree of medical certainty for up to seven days after immunization in previously normal children.⁹⁸ Specifically, we were able to show

95. L. Larson, "Report: Vaccine Might Trigger Reactions," *Am. Acad. Pediatr. News*, April 1994, 10, 116.

96. D. Miller, N. Madge, J. Diamond, J. Wadsworth, and E. Ross, "Pertussis Immunization and Serious Acute Neurological Illnesses in Children," *Br. Med. J.*, 1993, 307, 1171-76.

97. "New Pertussis Vaccine Ready to Begin Testing," *The Washington Post*, Health Section, 20 January 1987.

98. The 1991 IOM report (*Adverse Events*), pp. 344-45, stated:

To determine the relative and attributable risks of encephalopathy following [whole-cell] DPT immunization, the background incidence rate was estimated as follows. The four studies listed in Table 4-4 provide information on the total number of encephalopathy cases occurring in children of various ages . . . By pooling the results of the four studies in Table 4-4, the estimated background incidence rate for encephalopathy is estimated to be 78 per million children per year, or 0.43 per million children per 2-day period. By comparing the estimated total incidence in the 2 days postvaccination derived from all eight studies listed in Table D-2 with the estimated background incidence rate during the same period, the relative risk in the 2 days postvaccination can be estimated at 7.6 per million divided by 0.43 per million = 17.7. The attributable risk for encephalopathy is the difference between the total incidence and the background incidence: 7.6 per million - 0.43 per million = 7.2 per million. Assuming that children, on average, receive three immunizations, the estimated attributable risk of encephalopathy is 2.4 per million immunizations . . . using a background rate of 0.43 times 7 divided by 2 per million - 1.5 per million, the relative risk estimate is 7.6 and the attributable risk estimate is 3.3 per million immunizations.

These meta-analysis figures demonstrate that the risk of encephalopathy occurring within 7 days of a whole-cell DPT shot by random chance was 1.54 per million, which is far lower than the rate of encephalopathy following the whole-cell DPT shot (estimated at 3.3 per million). This allows the conclusion to be made, not with absolute certainty, but far more

that there was a greater than 77% association between whole-cell DTP vaccination and encephalopathies in comparison to the childhood background rate of encephalopathies for up to seven days after immunization with whole-cell DTP.

CONCLUSION: THE CURRENT SITUATION IN THE U.S.
AND OTHER COUNTRIES

The culmination of the legal challenges and accepted scientific evidence began in 1992 when the FDA approved the use of acellular DPT vaccine for the two booster shots given at eighteen months and five years of age. This was followed by FDA approval of the use of acellular DPT for the entire vaccination schedule in 1996. By the beginning of 2001, whole-cell pertussis vaccine had been completely removed from the American market. Interestingly, one of the sources for American acellular vaccine is the Japanese acellular DPT vaccine manufacturers, who have been producing and marketing it in Japan since the late 1970s. Lederle Laboratories purchases its acellular pertussis vaccine from Biken, while Connaught Laboratories buys its vaccine from Takeda. There are at least seven Japanese acellular pertussis producers.⁹⁹

Despite the previous literature on the subject and our findings, whole-cell pertussis vaccine continues to be licensed by the FDA. The central reason is that the overseas markets to which the United States manufacturers sell their vaccines demand the much cheaper whole-cell DPT version. The primary agency for buying and distributing the whole-cell DPT vaccine is the World Health Organization (WHO). It might seem to be an ethical violation for the United

likely than not, that in a child who had an encephalopathy within 7 days after a whole-cell DPT shot, it was far more likely due to the whole-cell DPT shot than the random association occurring in the population. It should be noted that it is generally agreed that a medically identifiable cause can be found in about 50% of these randomly occurring encephalopathies that occur in the first year of life. Therefore, in conclusion, from the meta-analysis published by the 1991 IOM, the probability of a case of encephalopathy being due to a random association is as follows: 0.43 per million per 2 days times 3.5 (since the reaction occurred within 7 days) divided by 2 (because half of the cases could be shown to have an identifiable cause) = 0.75 per million. The probability that the encephalopathy was caused by the whole-cell DPT shot from the same study is 3.3 per million. Therefore, from 0.75 divided by 3.3 multiplied by 100 it can be calculated that there was a 22.7% chance that the condition was caused by a random association with an encephalopathy unrelated to whole-cell DPT. It follows that there is a 77.3% chance that the encephalopathy was due to the whole-cell DPT shot.

99. "Vaccines in Japan 1986," F. Konosuke, Executive Director, Association of Biological Manufacturers in Japan. This article is in the authors' possession.

States to stop the use of whole-cell DPT vaccine domestically while selling it for use around the world. But WHO would be well advised to consider purchasing the acellular DPT vaccine for more than just the sake of ethics. According to the 1985 IOM committee, despite its initial higher cost, acellular DPT vaccine saves on overall medical costs.¹⁰⁰

The development and acceptance of acellular pertussis vaccine in the United States demonstrates that scientific evidence alone is not always enough to change harmful medical practices. Given the powerful resistance to change demonstrated by the pharmaceutical industry, it took years of litigation, consumer advocacy, international scientific development, and congressional action to create a new norm for childhood immunization. It would seem that open discussion of vaccine problems in the scientific and medical communities, along with policies that preclude those with a conflict of interest from determining vaccine policy, might help to prevent similar difficulties in the future in the rapidly expanding vaccination field.

100. U.S. Institute of Medicine, *Vaccine Development*.