Confronting "the strangler"

From ancient Greece to the 21st century, diphtheria has plagued humanity, continuing today despite effective vaccines.

BY CHRISTOPHER S. W. KOEHLER

Diphtheria is not something most people think about, at least in the developed world. One of many formerly deadly childhood diseases, it has been subdued through immunizations, which are usually combined with vaccines for tetanus and whooping cough. But in the early part of the 20th century, diphtheria was a common childhood illness in the United States and the rest of the world, and a leading cause of infant and child mortality. In the 1920s, when data were first gathered, roughly 150,000 cases were reported annually with 13,000 deaths.

By 1945, after immunization had been introduced, the number of cases dropped to 19,000 annually. By the late 1970s, fewer than 200 cases were reported annually, and no outbreaks have been reported in the United States since 1980. But the disease is still very much a fact of life—and death—in many parts of the world.

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A natural born killer

The Centers for Disease Control and Prevention describes diphtheria as "an upper respiratory tract illness characterized by sore throat, low-grade fever, and an adherent membrane of the tonsils, pharynx, and/or nose." The disease develops rapidly. After an incubation period of two to five days, a newly infected person feels general malaise with a headache, mild fever, sore throat, swelling of the neck, and tachycardia. Death can result from strangulation or from the effects of a toxin that often accompanies the disease.

Classic respiratory diphtheria is an infectious disease caused by *Corynebacterium diphtheriae*. The microorganism was first isolated in 1883 by Edwin Klebs, and one year later, Friedrich Loeffler, following Koch's postulates, showed it to be the cause of the disease.

The corynebacteria are Gram-positive aerobic nonmotile bacteria related to the actinomycetes. Unlike the latter, the corynebacteria do not form spores but instead depend on host organisms to spread. A diverse genus of bacteria, they include pathogens of both animals and plants. *C. diphtheriae* affects the respiratory tract of humans. By itself, *C. diphtheriae* causes little harm. But some cells can be infected by a bacterial virus (phage) and transformed into a deadly killer.

Diphtheria toxin—the toxin that causes the damage associated with the disease—is produced by strains of *C. diphtheriae* that have been genetically transformed by phages containing the toxin gene (tox+). Nontoxigenic strains of *C. diphtheriae* (tox–) cause only a mild disease. Tox– strains, however, can convert to tox+ strains in vivo when they encounter the appropriate bacteriophage.

Progression of the illness in an infected individual depends on whether the infecting strain is tox+ and on the health of the victim's immune system. Mild cases fade after a week, whereas more serious infections run from two to six weeks.

C. diphtheriae does not invade tissues generally, tending to concentrate in the epithelial cells of the respiratory system. It is there that the most serious of the superficial manifestations of infection by a tox+ strain is found: the formation of a characteristic pseudomembrane. This film is gray or white and consists of a coagulation of fibrin, white blood cells, dead respiratory epithelial cells, and rapidly reproducing *C. diphtheriae*. The membrane can adhere to the palate, pharynx, and trachea and may even extend down into the tracheobronchial pathways. The pseudomembrane can obstruct breathing and cause respiratory distress. In fact, before effective treatments were developed, the mortality rate from *C. diphtheriae* ranged from 35% to 90% in cases that affected the larynx.

Beyond the choking membrane (which led people in 17th-century Spain to call the disease "el garatillo"—the strangler), the peril of diphtheria infection lies in the systemic effects of the toxin. The toxin is absorbed by the lymphatic and circulatory systems and travels throughout the body. Its dissemination causes the most pathological effects of diphtheria infection.

Tissues vulnerable to the toxin include the heart and other muscles, nerves, the adrenal glands, the kidneys, the liver, and the spleen. If the disease is untreated, damage to these tissues and organs can be irreversible and cause death.

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History of treatment

The quest for a cure for diphtheria during the late 19th and early 20th centuries was part of the grand assault on infectious diseases initiated by Robert Koch in Germany and Louis Pasteur in France.

In 1887, Emil von Behring, a young physician in the German military, was posted by his government to the Pharmacological Institute at the University of Bonn to work as a bacteriologist. Not long afterward, he transferred to Robert Koch's Hygiene Institute in Berlin, where he worked as an assistant to Koch, whom he followed when the latter moved to the Institute for Infectious Diseases.

Von Behring's interest in diphtheria and other such maladies was triggered by a major outbreak of the disease in Germany in 1880 that he was forced to confront in his first year as a physician. The last decades of the 19th century proved to be one of the most exciting times in the history of microbiology, when researchers in Germany and France competed eagerly on the first truly scientific assaults on infectious disease.

From 1888 to 1890, Emile Roux and Alexander Yersin at the Pasteur Institute in Paris demonstrated that filtrates of diphtheria cultures contained no bacteria yet still caused damage characteristic of the disease. They determined that the filtrate contained a substance they called a toxin, which produced the symptoms of diphtheria when injected into test animals.

Before his stint at the University of Bonn, von Behring studied iodoform (CHI_3), a yellowish iodine compound used as an antiseptic. He concluded that although it did not kill microorganisms, it could neutralize their effects. On the basis of those observations, in 1890 Behring and Japanese researcher Shibasaburo Kitasato (who was instrumental in demonstrating the bacterial nature of bubonic plague) tried to determine whether injecting an organism treated by disinfectants might clear the subject of microorganisms. They performed the experiments with tetanus and diphtheria. Von Behring and Kitasato discovered that blood from animals that had survived an infectious disease could be used to treat other animals infected with the same malady. These injections produced substances that would neutralize poisons produced by bacteria. They termed these "antitoxins". They also found that these antitoxins could cure an animal displaying symptoms of diphtheria poisoning, conclusions soon duplicated by other researchers. For his work on diphtheria, Bering received the Nobel Prize in Physiology or Medicine in 1901, among many other scientific and civil accolades.

In 1907, Theobald Smith, an American, suggested that mixtures of toxins and antitoxins could be used to immunize humans against diphtheria, and in 1913 von Behring produced such a concoction. He refined this, and his work resulted in the modern methods of inoculation that have served to largely banish diphtheria from the industrialized world. The use of antitoxins in the treatment of diphtheria cut the mortality rate, at least in developed countries, to 5% or lower. Since von Behring's time, toxoids, nonlethal forms of the diphtheria toxin, have lowered mortality even more. Given to children less than seven years old in a series of three injections (along with vaccines for tetanus and whooping cough), the toxoids confer artificial immunity. Immunization has proven even better than treatment with antitoxins because it reduces susceptibility to diphtheria and severity should infection occur.

Back to the future?

Diphtheria has, for the time being, ceased to be a major concern in the United States, although it has not entirely vanished. In the waning years of the 20th century, there were still cases of diphtheria, albeit only 25 or so annually. Although people who have not been immunized or whose immunities have not been bolstered with booster shots are still susceptible, as are the immunocompromised, the movement against childhood immunization may well exacerbate this risk.

The situation, however, is rosy compared with other parts of the world. China, Algeria, and Ecuador have experienced diphtheria outbreaks in recent years. But perhaps the chief danger is in the former Soviet Union.

In 1990, a diphtheria epidemic broke out in Russia and spread to the rest of the Commonwealth of Independent States (CIS) by the end of 1994. More than 150,000 cases have been reported, along with 5000 deaths in the CIS between 1990 and 1998. Although massive immunization drives have controlled the epidemic, thousands of new cases are still being reported, and a risk of diphtheria infection remains in all the former Eastern Bloc countries.

Further reading

Association of State and Territorial Directors of Health Promotion and Public Health Education. Diphtheria; www.astdhpphe.org/infect/dip.html.

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