Division of Biologics Standards
Lab of Viral Immunology

From the Laboratory of Hygiene to CBER

The regulation of biologics and the research necessary to support such regulation was delegated to the U.S. Treasury Department's Hygienic Laboratory of the Public Health and Marine Hospital Service, under the provisions of the Biologics Control Act of 1902. As the Hygienic Laboratory evolved into the CBER of today, its name also evolved to reflect changing responsibilities. The progression of names is given here. These names are used throughout the publication.

Dr. Ida Bengtson, bacteriologist in the Hygienic Laboratory, 1916
Courtesy of National Library of Medicine

1887 **Laboratory of Hygiene** of the Marine Hospital Service (MHS)

1891 Laboratory of Hygiene renamed **Hygienic Laboratory**, still of the MHS

1902 **Hygienic Laboratory** of the Public Health and Marine Hospital Service (PH-MHS)

1930 Hygienic Laboratory renamed **National Institute of Health** (NIH)

1937 **Division of Biologics Control** (DBC) formed within NIH

1944 DBC renamed **Laboratory of Biologics Control** (LBC)

1948 LBC incorporated into **National Microbiological Institute** (NMI), NIH

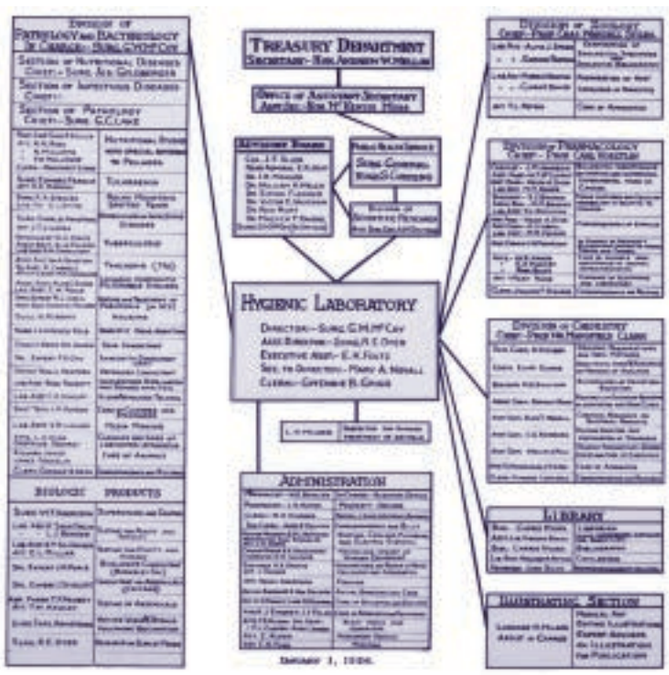
1955 LBC becomes **Division of Biologics Standards** (DBS), an independent entity within NIH; NMI renamed the National Institute of Allergy and Infectious Diseases

1972 DBS transferred from NIH to FDA; becomes **Bureau of Biologics** (BoB)

1982 BoB merged with Bureau of Drugs to form **National Center for Drugs and Biologics** (NCDB)

1983 Biologics component of NCDB renamed **Office of Biologics Research and Review** (OBRR) within Center for Drugs and Biologics (CDB)

1988 CDB separated into two Centers; **Center for Biologics Evaluation and Research** (CBER) (formerly OBRR) and Center for Drug Evaluation and Research (CDER)



U. S. Treasury Organizational Chart, 1926
Courtesy of National Library of Medicine

Dedication ceremony of Building 29. Dr. Roderick Murray greets the King and Queen of Thailand. DHEW Secretary Arthur Flemming looks on.

The Beginning of Biologics

Imagine living in the mid-18th century, when infectious disease epidemics were common and survival depended solely on a person's resistance—the body's natural ability to fight back against disease-causing bacteria and viruses. Imagine not knowing that tiny, unseen disease agents exist and that, although most are harmless, some are pathogens that cause infectious human diseases such as smallpox, cholera, rabies, diphtheria, plague, typhoid, tuberculosis, and many others. We who live in the 21st century are fortunate that the existence of a pathogen-disease relationship has been recognized, allowing biomedical science to make enormous strides leading to the prevention of many infectious diseases.

Above, right
Medieval alchemist
Courtesy of National Library of Medicine

Below, right
House sign, ca. 1910-1919
Courtesy of National Library of Medicine

Cholera, one of the most feared epidemic diseases of the 19th century
Courtesy of National Library of Medicine

Vaccination from the Calf
Courtesy of National Library of Medicine

The Speckled Monster

Smallpox (the "speckled monster") was a feared infectious disease that was frequently fatal. Smallpox caused about 10 percent of all deaths in 18th-century Europe; in London, about 80 percent of children younger than five who developed smallpox died. Early on, people noticed that those who survived smallpox seemed to be protected against the disease. Based on this observation, they often used the practice of "variolation"—putting pus or ground scabs from a person with mild smallpox into a healthy person, through the nose or skin. The practice of variolation was introduced into England in 1717. In 1721, it was first used in North America to stop a smallpox epidemic in Boston. These variolation efforts were carried out by Zabdiel Boylston, MD, who showed that the risk for death from variolation was about 2%. The risk of death from smallpox was about 15%. Many were reluctant to use the procedure, including Benjamin Franklin, whose 4-year-old son died of smallpox in 1736. However, after seeing the procedure's effectiveness, Franklin became an advocate for variolation and for educating the public about it through simple written materials.

In 1796, in a historic scientific breakthrough, the English physician Edward Jenner discovered that immunity to smallpox could be achieved by deliberately infecting a person with cowpox, a mild disease that did not have the serious side effects of variolation. This was the first "vaccination." By 1800, Jenner's vaccination technique for smallpox had spread to Europe and Benjamin Waterhouse had introduced the technique into the United States, where it became widely used in Boston, New York, Philadelphia, and Baltimore.

To help prevent fake smallpox vaccine from being marketed, James Smith, a Baltimore physician, persuaded Congress to pass The Vaccine Act of 1813—the first federal law for any medical substance. The Act authorized the President to appoint a smallpox "vaccine agent" who would preserve and furnish "genuine vaccine matter" to people who requested it. The Act was repealed in 1822, however, returning smallpox vaccine control to local authorities, after vaccine furnished by Smith (the first and only vaccine agent) was believed to have been the cause of an outbreak of smallpox in North Carolina.

Early Research in Bacteriology

Between 1800 and 1900, many great scientists from various countries conducted innovative, sometimes controversial experiments leading to discoveries that were critical for developing biologics to prevent disease. In the second half of the 19th century, French chemist and microbiologist Louis Pasteur and German physician Robert Koch laid the foundation for the science of bacteriology and its application. Pasteur showed that microorganisms were required for fermentation and deterioration of foods and beverages. Also, he isolated the bacteria for certain silkworm diseases. In a major advance in 1879, he prepared the first laboratory-produced vaccine by using weakened chicken cholera bacteria to protect fowl against the disease. At about the same time, Koch was investigating the cause of anthrax. He perfected pure-culture techniques to isolate the anthrax bacterium and proved that it caused anthrax disease in laboratory animals. Using

Koch's discovery to good advantage, Pasteur developed a weakened-bacterium anthrax vaccine in 1881 that protected animals. He then turned his attention to rabies, for which he developed an effective weakened-virus vaccine in 1885.

While Pasteur was doing vaccine research, Koch was concentrating on identifying disease bacteria; he isolated the organisms that caused tuberculosis (1882) and cholera (1883). In 1884, he published a paper on the tuberculosis organism that described the steps necessary to establish its pathogenic nature, steps now known as "Koch's postulates." These included: demonstrating the presence (by staining) of the organism in tubercular lesions in various human and animal organs; cultivating the organism in pure culture in blood serum; and producing tuberculosis at will by inoculating guinea pigs with the organism.

Robert Koch, 1932
Courtesy of National Library of Medicine

U.S. scientists also were doing bacteriology research during this period. American bacteriologists Theobald Smith and Edmund Salmon introduced a new vaccine concept by preparing an effective vaccine from hog cholera bacteria killed by heat. Their work on "killed-bacterium vaccines," published in 1886, led to the development of human "killed" vaccines for typhoid, cholera, and plague by the beginning of the 20th century.

Right
Edward Jenner
Courtesy of Blocker Medical Library, The University of Texas Medical Branch, Galveston, Texas

Edward Jenner prepares to inoculate a young woman, 1802

The First Smallpox Vaccination Experiment

In 1796, Edward Jenner, a rural physician in Gloucestershire, England, made the first scientific attempt to control smallpox by deliberate inoculation—a term we now understand to mean introducing a disease-causing organism into a person to stimulate the production of antibodies protective for the disease. Jenner based his experiment on observations that people who had suffered an attack of cowpox, a harmless disease contracted from cattle, did not later develop smallpox. He used an inoculation procedure that was extremely rudimentary compared with modern-day techniques. He took pus from cowpox lesions on the hand of a dairymaid, Sarah Nelmes, and "inoculated" an 8-year-old boy, Thomas Phipps, by putting the material into two cuts on his arm. The boy became slightly ill over the next nine days and recovered by the tenth day. Six weeks later, Jenner "inoculated" the boy with pus from smallpox lesions. As Jenner had hoped, the boy did not develop smallpox. He concluded that cowpox protected against smallpox. In other experiments, he later showed that cowpox could be deliberately transmitted from person to person as a way of providing protection. Jenner called the cowpox material vaccine, from the Latin vacca (cow), and called the process vaccination. In 1798, he published a book entitled An Inquiry Into the Causes and Effects of the Variolae Vaccinae *that described his vaccination results. In his book, Jenner states, "Thus far have I proceeded in an inquiry founded...on the basis of experiment;...I shall myself continue to prosecute this inquiry, encouraged by the hope of its becoming essentially beneficial to mankind." Despite some opposition and failures caused by not following Jenner's procedure correctly, vaccination for smallpox quickly became an accepted practice. Dr. Benjamin Waterhouse introduced smallpox vaccination into the United States (Boston) in 1800.*

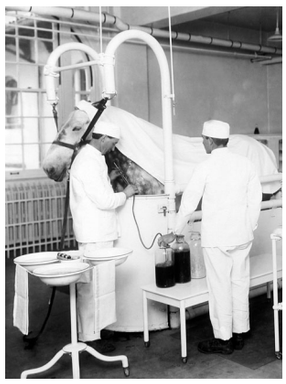
Investigating Disease Immunity

During the years when some scientists were identifying bacterial causes of disease and developing disease vaccines, others were trying to explain what happens in the body to produce disease immunity. In 1884, Ilya Metchnikoff (Russian) showed that certain body cells (phagocytes) consumed and destroyed invading bacteria and other foreign proteins (antigens) and proposed his theory of "cellular immunity." In 1891, Paul Ehrlich (German) suggested that antibodies (molecules formed by the body to attack antigens) also have a key role in immunity and later pointed out that active and passive immunity differ. Active immunity is acquired when the body's own tissues produce antibodies against a disease, resulting from either an attack of or exposure to the disease, or from inoculation of a vaccine consisting of weakened or killed pathogens. Passive immunity is acquired when people are injected with the antibodies themselves, which may be of animal or human origin.

Louis Pasteur: An Extraordinary 19th Century Scientist

Louis Pasteur, a French chemist and microbiologist, was an extremely skillful scientist who made significant contributions to human health and coincidentally to the 19th-century wine, beer, and silk industries. His experiments helped to lay the groundwork for bacteriology—the science of bacteria and their relationship to medicine, industry, and agriculture. Pasteur proved that microorganisms cause fermentation, a chemical change that produces alcohol and carbon dioxide. He disproved the theory of "spontaneous generation," the concept that bacterial life arose spontaneously. Also, he developed the process that came to be known as pasteurization, which is the destruction of harmful bacteria by heat, and developed vaccines for chicken cholera, anthrax, and rabies. In 1879, Pasteur left a chicken cholera culture exposed to air over a long summer holiday. He found that the culture, when weakened by exposure to air, protected fowl inoculated with it against chicken cholera. This was the first vaccine developed in a laboratory. At the same time, Pasteur was developing a vaccine for the anthrax bacterium. In a well-controlled experiment in 1881, Pasteur inoculated 24 sheep, one goat, and six cows with weakened anthrax bacteria. All of the animals remained healthy. He then challenged these animals, and others that had not been inoculated, with the virulent anthrax. In this experiment, he showed that all inoculated animals remained alive, whereas the uninoculated animals died. Pasteur's work with the chicken cholera and anthrax vaccines demonstrated that it was possible to use systematic procedures to make reproducible vaccines. His research on a rabies vaccine began in 1886. Using brain tissue from infected dogs, Pasteur developed a weakened rabies virus that he used in 1886 to inoculate a nine-year-old boy, Joseph Meister, who had been bitten by a rabid dog. Introducing an actual disease virus, even a weakened virus, into a human was highly controversial at the time. However, the experiment with Joseph Meister was a clear success that was confirmed by many subsequent successes and that helped save many others from rabies.

Louis Pasteur
Courtesy of Blocker Medical Library, The University of Texas Medical Branch, Galveston, Texas



Production of diphtheria antitoxin by inoculating horses required great care to maintain purity and avoid contamination
Courtesy of National Archives and Records Administration

Serum therapy, a practical application of passive immunity, proved to be a valuable approach for fighting diphtheria, a major cause of illness and death before the 20th century. At the Pasteur Institute in 1888, Emile Roux and Alexandre Yersin isolated a powerful toxin from the diphtheria bacterium and showed that it harmed tissues and organs. This paved the way for the work of Emil von Behring and Shibasaburo Kitasato at Koch's laboratory in Berlin. In 1890, they found that injecting a small dose of diphtheria toxin (an antigen) into animals produced a serum containing antitoxins (antibodies) that provided immunity to people inoculated with the serum. In 1894, Roux reported that large quantities of diphtheria antitoxins could be produced in horses. Large-scale production and use of the antitoxin serum began in Europe at this time. The first biological standard in the world, a diphtheria antitoxin serum reference standard, was prepared by Paul Ehrlich in 1897.

Production of diphtheria antitoxin
Courtesy of National Archives and Records Administration

The First Heat-Killed Vaccine

Vaccines made from killed or inactivated microorganisms are safer than attenuated vaccines, which are made from weakened, but live, microorganisms. There is a small chance that an attenuated vaccine might cause the disease it is designed to prevent. Therefore, development of the first heat-killed vaccine—a vaccine prepared from microorganisms killed by elevated temperature—was a major step in vaccine development. This took place in the United States in the mid-1880s, through the efforts of Theobald Smith and Edmund Salmon. They developed a heat-killed vaccine from the bacterium that causes hog cholera. The vaccine, tested by injecting it into pigeons, was found to be effective in protecting the birds against the disease. Smith and Salmon, who were working for the U.S. Department of Agriculture at the time of their discovery, published their work on the heat-killed hog cholera vaccine in 1886. As sometimes happens in research, scientists from Pasteur's laboratory in Paris independently published an article on heat-killed vaccines in late 1887, about 16 months after the report of Smith and Salmon. The original work on heat-killed vaccines proved to be highly valuable and led to the development of killed vaccines for several human infectious diseases—typhoid, cholera, and plague—in the late 1890s.

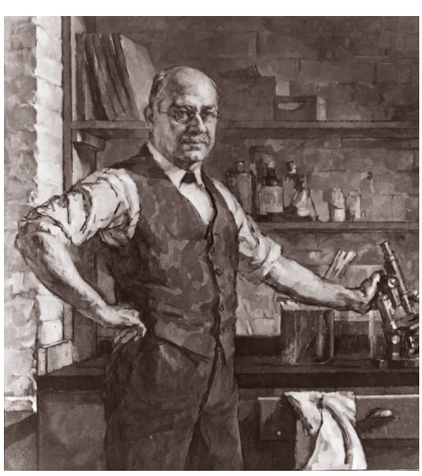
U. S. Marine Hospital No. 21, NY
Courtesy of National Library of Medicine

The Public Health Service Hygienic Laboratory

The Marine Hospital Service (MHS), the original public health agency, was established in 1798 to provide hospital care for merchant seamen. It also protected port cities against diseases such as smallpox, cholera, and yellow fever. Joseph Kinyoun was a young MHS medical officer who toured the research centers of Europe to learn the latest techniques for controlling infectious diseases. Determined to apply his new-found knowledge to improving public health in the United States, he established one of the country's first bacteriological laboratories in 1887 in the MHS Marine Hospital on Staten Island, New York. This one-room "Laboratory of Hygiene," with Kinyoun as director, was the beginning of medical laboratory research in the U.S. Public Health Service. In 1891, the Laboratory of Hygiene was moved to Washington, D.C. and renamed the "Hygienic Laboratory." Soon after, Kinyoun again visited Europe and, at the Pasteur Institute in Paris, learned the procedure for preparing diphtheria antitoxin. On returning to the United States, he prepared an antitoxin serum to be used by the MHS and demonstrated its production to representatives of local and state health boards. In a report to the U.S. Surgeon General in 1895, Kinyoun noted that all serum intended for sale should be made and tested by competent and disinterested persons, making an early plea for the establishment of a regulatory service. Beginning in 1899, under new director Milton Rosenau, the Hygienic Laboratory expanded into a research organization with divisions of chemistry, bacteriology and pathology, zoology, and pharmacology. Recognizing its importance, Congress authorized $35,000 in 1901 for construction of a new building, in which the Laboratory could investigate "infectious and contagious diseases and matters pertaining to the public health." The Hygienic Laboratory ultimately evolved into the National Institute of Health.

Officials and scientists in the United States had paid close attention to the compelling evidence presented in Europe that specific microorganisms caused specific infectious diseases and to the vaccination techniques developed to control these diseases. Joseph Kinyoun, a medical officer in the Marine Health Service, played a key role in bringing this new technology to America.

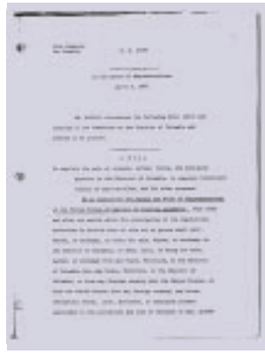
As the end of the 19th century neared, scientists had identified almost two dozen disease pathogens and introduced many fundamental concepts of bacteriology, vaccinology, and immunology to biomedical research. The state of the science at this time provided a strong research base for further development of biologics.



Joseph J. Kinyoun, MD, founder of the Hygienic Laboratory
Courtesy of National Institutes of Health

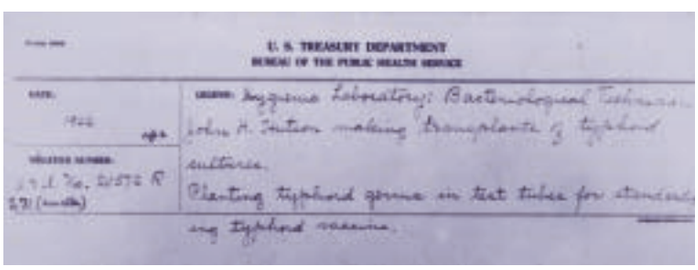
Refluz Apparatus. Used in 1970's to early 1980's by a team of biochemists under Dr. Darrell Liu to determine the amino acid sequence of proteins, and the structure of bacterial polysaccharides used in vaccines.

Virus-Toxin Law (Biologics Control Act), 1902



The Early Years of Biologics Regulation and Development

The discoveries in bacteriology, vaccinology, and immunology that were taking place at the brink of the 20th century were tremendously exciting. Equally exciting to many was the prospect of being able to apply these discoveries to prevent and treat dangerous diseases. Live vaccines were being used worldwide for smallpox and rabies, heat-killed vaccines for cholera, typhoid, and plague, and antitoxins for diphtheria and tetanus. The results were dramatic. In large U.S. cities, for example, the number of deaths from diphtheria decreased by 50 to 70 percent between the early 1890s and the early 1900s, and by more than 99 percent by the early 1940s. In the Spanish-American War of 1898, 1 in 5 American soldiers had typhoid fever. During World War I, only 1 in 2000 developed this disease. And, in World War I in 1914, tetanus occurred in 8 per 1,000 wounded British soldiers. After development of routine tetanus antitoxin use and careful wound management, however, this rate fell to 1.5 per 1,000. U.S. forces entering the war in 1917 benefited from the British experience, and had a tetanus incidence of only 0.16 per 1,000 wounded.


U. S. TREASURY DEPARTMENT
BUREAU OF THE PUBLIC HEALTH SERVICE

Old Public Health Service record of typhoid culture

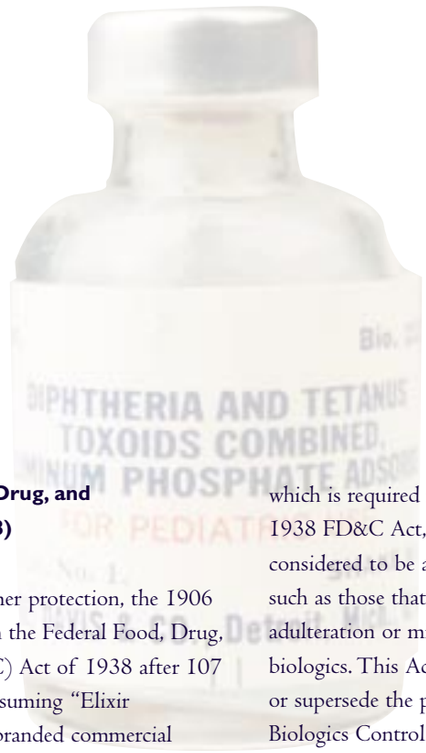
By 1895, laws regulating biologics had been enacted by the governments of France, Germany, Italy, and Russia. In part, these laws dealt with licensing and inspection of products by government-approved laboratories, proper labeling, and the accreditation of manufacturing facilities. In the United States, even though many were concerned about the safety of biologics—because they were injected and could have a rapid adverse effect if contaminated—the rush to use these products proceeded without regulatory safeguards. Legislators acted after a tragedy occurred in October 1901, when 13 children in St. Louis died after being given diphtheria antitoxin that was contaminated with tetanus.

The Biologics Control Act (1902)

As a result of the St. Louis tetanus outbreak and similar (but smaller) occurrences of contaminated smallpox vaccine and diphtheria antitoxin, Congress passed the Biologics Control Act on July 1, 1902, only a few months after it was proposed—with virtually no debate or opposition. This Act authorized the Hygienic Laboratory of the Public Health and Marine Hospital Service to issue regulations that governed all aspects of commercial production of vaccines, serums, toxins, antitoxins, and similar products, with the objective of ensuring their safety, purity, and potency. The Laboratory issued its first series of regulations in 1903 and additional regulations in 1909 and thereafter, to strengthen control over biologics production. Further, in 1934, the Hygienic Laboratory—renamed the National Institute of Health in 1930 by the Ransdell Act—issued a regulation stating that licenses to manufacture new biologics would not be granted without evidence that the products were effective. Overall, however, the basic provisions of the 1902 Act served the nation well throughout the 20th century.

The Federal Food and Drugs Act (1906)

In 1906, the Federal Food and Drugs Act outlawed adulterated and misbranded foods and drugs, but made no specific reference to biologic drugs. In contrast to the quick passage of the 1902 Act, there had been 25 years of heated debate before Upton Sinclair's 1906 novel, *The Jungle*, which described the unsanitary conditions in Chicago's meatpacking industry, caused a public furor that helped pass the law. The 1906 Act had some shortcomings. For example, the Supreme Court, in a case involving "Dr. Johnson's Mild Combination Treatment for Cancer," ruled in 1911 that the Act did not prohibit false therapeutic claims, but only false and misleading statements about the ingredients or identity of a drug. As a result, Congress passed the Sherley Amendment in 1912, which prohibited labeling medicines with false therapeutic claims intended to defraud the purchaser, a legal standard difficult to prove.



The Federal Food, Drug, and Cosmetic Act (1938)

To strengthen consumer protection, the 1906 Act was replaced with the Federal Food, Drug, and Cosmetic (FD&C) Act of 1938 after 107 people died from consuming "Elixir Sulfanilamide," a misbranded commercial product that had been made using toxic diethylene glycol as a solvent instead of alcohol, which is required in an "elixir." Under the 1938 FD&C Act, a biological product was considered to be a drug, and parts of the Act, such as those that concerned drug or device adulteration or misbranding, were applied to biologics. This Act, however, did not modify or supersede the provisions of the 1902 Biologics Control Act. After 1938, the appropriate provisions of both Acts were used to regulate biologics.

The St. Louis Tetanus Epidemic

Diphtheria antitoxin was a formidable new weapon in the fight against diphtheria, a dangerous infectious disease. But without proper standards to ensure its potency and purity, the antitoxin could be harmful instead of beneficial. Medical workers and the public expressed concern about the poor supervision of antitoxin production, and the lack of inspection and testing of the final product. Even though many believed that federal oversight was necessary, no action was taken until a tragedy occurred. In 1901, when a serious diphtheria epidemic swept St. Louis, Missouri, victims of the disease were given antitoxin serum prepared from horses. In late October, five-year-old Veronica Neill was admitted to the city hospital and received two shots of diphtheria antitoxin. Several days later, on October 26, she died from tetanus, a different infectious disease. Her doctor notified the St. Louis Health Commissioner that her death likely was caused by tetanus-contaminated antitoxin prepared by the city's Health Department. Distribution of the antitoxin was stopped immediately. An investigation uncovered that a horse named Jim, which had provided diphtheria antitoxin for three years, had contracted tetanus and had been killed. The contaminated serum from this horse should have been destroyed, but was not. Instead, it was accidently bottled and issued to doctors to use in treating diphtheria patients. Thirteen children died from tetanus as a result of receiving this serum. Although the St. Louis disaster was the worst, it was not the only such incident. Also in the fall of 1901, nine children in Camden, New Jersey, died from tetanus as a result of receiving contaminated smallpox vaccine. These events spurred Congress into action. The Biologics Control Act was passed quickly and without notable opposition, and signed into law by President Theodore Roosevelt on July 1, 1902.

Courtesy of National Library of Medicine


LICENSE

First biologics license, Parke, Davis and Company, 1903
Courtesy of Pfizer, Inc.


MANUFACTURE OF VIRUSES, SERUMS, TOXINS AND ANALOGOUS PRODUCTS.

Second biologics license, H. K. Mulford, Co.
Courtesy of Merck & Co., Inc.

The Biologics Control Act of 1902

In 1901, there were no mandatory federal manufacturing or product standards for biologics. The deaths of 13 children in St. Louis in 1901 as a result of receiving tetanus-contaminated diphtheria antitoxin, and other similar incidents, prompted quick action by lawmakers. The Biologics Control Act (also called the Virus-Toxin Law) was passed on July 1, 1902, with little comment or publicity. The Act mandated annual licensing of establishments to manufacture and sell vaccines, sera, antitoxins, and similar products in interstate commerce. Biologics had to be labeled with the name of the product, the name, address, and license number of the manufacturer, and an expiration date for potency. Production of biologics had to be supervised by a qualified scientist. The Hygienic Laboratory of the Public Health and Marine Hospital Service was authorized to conduct regular inspections of licensed manufacturing establishments and to sample products on the open market for purity and potency. The Act included provisions for revocation or suspension of licenses and for penalties in cases of violations. Most important, the Act empowered the government to issue rules necessary to enforce the Act. The first regulations under the Act, which dealt with the issuance of licenses and inspection, became effective on August 21, 1903. By 1904, 13 establishments had been inspected and licensed, mostly for the sale of smallpox vaccine and diphtheria antitoxin. The Hygienic Laboratory tested the products of licensed establishments for purity and potency once a month. The Act stimulated the growth of the Hygienic Laboratory. Between 1904 and 1921, the number of staff increased from 13 to 127 and the number of products monitored climbed to 102. Overall, the Act improved the quality of biologic products in the marketplace, helped to restore confidence in these products, stimulated research on biologics, and promoted mutual respect and cooperation between the federal government and the pharmaceutical industry.

Implementing the Biologics Control Act

Between 1903 and 1907, the Hygienic Laboratory established standards and issued licenses to pharmaceutical firms for making smallpox and rabies vaccines, diphtheria and tetanus antitoxins, and various antibacterial antiserums. After 1907, many firms also started producing antibacterial vaccines. Beginning in 1917, the Laboratory issued licenses for making toxin products that provided immunity, for example: diphtheria toxin mixed with antitoxin [1917]; scarlet fever toxin [1925]; diphtheria toxoid [1926]; tetanus toxoid [1933]; additional antitoxins such as botulinum [1921], scarlet fever streptococcus [1925], gonococcus [1927], and perfringens and other gas gangrene-causing bacteria [1931-1939]; and human bacterial and viral antisera for pertussis, poliomyelitis, and mumps [1939-1941].

Throughout these early years, as is still true today, the 1902 Act stimulated scientific research by the Hygienic Laboratory to improve existing biologics and find better ways of producing them, to develop standards for new products, and to find immunizing agents for all infectious diseases. Laboratory staff made numerous significant contributions that advanced the state of the science. For instance, staff established the standards for botulinum antitoxins and for gas gangrene antitoxins, developed a practical method for preparing serums to diagnose various types of pneumonia, and developed an improved meningitis serum potency test as well as a serum specific for different types of meningitis bacteria.

Blood-letting
Courtesy of National Library of Medicine

Margaret Pittman and visitors to her lab

Early Blood Research

In addition to vaccines and antitoxins, the Hygienic Laboratory's regulatory responsibilities extended to blood and any products made from blood. During the first few decades of the 20th century, scientists learned much about how to use blood properly for medical purposes. Early attempts at transfusion led to serious adverse reactions. However, in 1901, Austrian scientist Karl Landsteiner discovered that individuals belonged to one of four different blood groups (O, A, B, and AB), and that transfusions between people in different blood groups could be unsafe. In addition, scientists developed suitable techniques for collecting blood, separating the plasma, and properly storing these products. In 1934, the Laboratory—by then named the National Institute of Health—issued the first licenses to manufacturers for production of a human blood product. The product was a preparation of protein (called immunoglobulin G or IgG in current terminology) from human placental extracts, and was used for prevention of measles.

The considerable progress made in effectively regulating and developing biologics during the first four decades of the 20th century was put to the test with the entry of the United States into World War II in 1941.

Karl Landsteiner
Courtesy of National Library of Medicine

Pioneering Work on Haemophilus influenzae

Haemophilus influenzae bacteria cause infections in humans ranging from asymptomatic respiratory infections to serious diseases such as meningitis. Children are particularly susceptible to this pathogen. In the early 1930s, Margaret Pittman, who retired from the Division of Biologics Standards in 1971 after 35 years of making significant scientific contributions, was doing postgraduate work at the Rockefeller Institute (RI) for Medical Research. While at the RI, she conducted pioneering research on the microbiology and immunology of infections caused by H. influenzae. She found that these bacteria existed in two forms—encapsulated (with a special coating) and unencapsulated. The unencapsulated bacteria, which generally caused either no illness at all or relatively mild respiratory infections and mucosal infections (such as sinusitis), frequently were found in the upper respiratory tract of adults. Pittman discovered six different varieties of the encapsulated H. influenzae organism and observed that only the type b encapsulated variety seemed to cause serious diseases in children, for example, meningitis, pneumonia, and septic arthritis. She identified the material forming the coating of the type b encapsulated variety as a certain polysaccharide, information that would be useful in developing future vaccines. Pittman's work formed the basis for development of an antiserum for invasive H. influenzae type b disease by Hattie Alexander and colleagues at the Columbia University College of Physicians and Surgeons, in the late 1930s. The antiserum was the first effective therapy for this potentially fatal infection. The 1985 licensing of a polysaccharide vaccine for H. influenzae type b, for use in preschool-aged children, was a long-term outcome of Pittman's early research on this pathogen. Research by John Robbins, MD, and colleagues, conducted at the Bureau of Biologics in the 1970s – 1980s, led to development and licensing in 1987 of a polysaccharide-protein conjugate vaccine for H. influenzae type b that provided protection for infants, the group most at risk for disease. In 1996, Robbins and Rachel Schneerson, MD, received the Albert Lasker Award for Clinical Medical Research for their work on the conjugate vaccine.

Above
John Robbins and Rachel Schneerson, winners of the Lasker Award, 1996
Courtesy of National Institutes of Health

Bernice Eddy, PhD

Early Research on Influenza Vaccine

The influenza (flu) epidemic of 1918-19 caused an estimated 20 million deaths worldwide. There was little progress, however, in flu research until a flu virus called Type A was finally isolated in England in 1933 and in the United States in 1934. This advance came from the use of embryonated chicken eggs for recovering the virus—a new breakthrough that allowed the preparation of vaccines. The most common varieties of flu are caused by the Type A flu virus. Researchers discovered a second kind of flu virus (Type B) in the 1940 flu epidemic. Flu vaccines made in the late 1930s and early 1940s were not always effective, because no accurate test was available to measure their potency. Even though flu vaccine was not yet licensed for marketing, commercial laboratories produced large amounts of flu vaccine for the U.S. Army during World War II. Because this vaccine was of variable quality, Bernice Eddy, a scientist at the Division of Biologics Control, concentrated on developing the first reliable potency test for flu vaccine, so that manufacturers could make a uniform product with the desired effectiveness. The vaccine produced during World War II was effective against both Type A and Type B influenza viruses. The flu vaccine was licensed in 1945 and, after World War II, it was also used for civilians. Producing effective flu vaccine is complicated because the Type A virus has a number of subtypes and, as new subtypes appear and circulate in the human population, vaccine formulations must be changed to protect people against the new subtypes. Today's flu vaccines are 70 to 90 percent effective in reducing a person's chances of getting the flu.

World War II poster, 1941-1945
Courtesy of National Archives and Records Administration

World War II and the Postwar Period

Many of the scientific advances in the early 1940s were driven by the need to provide U.S. military personnel in World War II with the best medical care possible, including ready access to safe blood products and the best possible protection against disease.

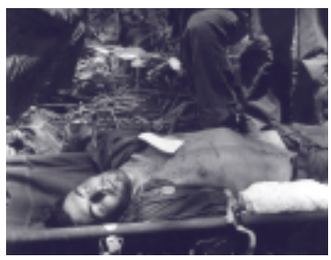
Developing Essential Blood Products

In 1940, shortly after the start of the German offensive in Europe and at the request of American Red Cross, American biochemist Edwin Cohn and his Harvard colleagues began to develop methods for blood fractionation, the separation of blood plasma proteins. By the summer of 1941, using alcohol-water mixtures, they were able to prepare albumin, globulins, fibrinogen, and fibrin—all useful blood proteins. The albumin was particularly important, because it could be given to the wounded to restore blood volume, reducing the risk of shock resulting from blood loss. On December 7, 1941, a small supply of albumin was on hand, which was immediately flown to Pearl Harbor where it proved to be extremely beneficial to people suffering from shock and low blood protein as a result of severe burns.

During World War II, the Division of Biologics Control established standards for manufacturing plasma and albumin, and supervised their production in commercial establishments. The Division issued licenses for several blood fractionation products, including albumin, globulins useful for blood grouping, immune globulins (called gamma globulin at the time), fibrin foam and thrombin (clotting agents used to control bleeding during surgery), and fibrin film (used in surgery as a substitute for the outermost membrane covering the brain).

In 1940, almost four decades after the discovery of the A, B, O, and AB blood groups, Karl Landsteiner and Alexander Wiener found another important characteristic of blood—a protein called the Rh (rhesus) factor—in the blood of rhesus monkeys. The Rh factor is also present in humans in 85 percent of Caucasians, and in an even larger percentage of African Americans and Asians. If blood from a person with the Rh factor (Rh positive) is transfused into a person without the Rh factor (Rh negative), antibodies can form in the Rh-negative person that cause the Rh-positive blood cells to clump together and eventually be destroyed. If the Rh-negative person is given additional transfusions of Rh-positive blood, the concentration of antibodies may become high enough to cause a serious or fatal reaction. Thus, in addition to knowing a person's A, B, O, or AB blood group, it is important to know whether the Rh factor is present. The Laboratory of Biologics Control issued the first licenses for Rh typing serums in 1947.

American troops wait for medical treatment, Normandy, 1944
Courtesy of National Archives and Records Administration



Wounded soldier after receiving blood plasma, 1944
Courtesy of National Archives and Records Administration

World War II soldier receiving blood plasma infusion, 1945
Courtesy, National Archives and Records Administration

Elimination of Jaundice Virus From Blood Plasma

During World War II, the demand for human blood plasma (the liquid portion of the blood in which the solid components are suspended) for America's military personnel was huge. The Division of Biologics Control (DBC) had responsibility for setting up safety standards and supervising the production of blood products by commercial laboratories. Blood plasma, blood serum (plasma in which fibrinogen, a clotting agent, has been "used up" by clotting the blood), and serum albumin (a protein) were among these products. Although blood products without doubt saved many lives, they were found to have potential hazards. In 1942, 28,000 military personnel, injected with a yellow fever vaccine prepared with human blood serum as a stabilizing agent, developed a disease then named jaundice. Obvious symptoms were yellowing of the skin and eyes. One hundred people died. There was a strong possibility that some unknown factor in human blood was causing the disease. Thus, in the middle of wartime production of blood plasma on a massive scale, the DBC was faced with the urgent need to find a way to guarantee its safety. By conducting careful research, three DBC scientists, John Oliphant, Alexander Gilliam, and Carl Larson, showed that people who were inoculated with blood serum from jaundice-infected patients also developed jaundice, but that the disease was not spread by personal contact. The cause of the jaundice appeared to be an unidentified virus. The yellow fever vaccine likely had been contaminated by the blood serum of donors who either had unrecognized disease or were simply carriers of the virus. Because blood plasma from individual donors was generally "pooled," one donor infected with the virus could contaminate an entire batch of either plasma or serum derived from the plasma. The DBC scientists found that the jaundice-causing virus was heat resistant. Also, it was too small to be removed from blood products by using filters. Next, Oliphant, working with biophysicist Alexander Hollaender, conducted research in which ultraviolet radiation appeared to kill the virus in blood serum and plasma. In April 1949, regulations were issued by the Laboratory of Biologics Control (LBC) requiring that human blood plasma and serum be irradiated. Studies conducted by Oliphant and Roderick Murray in the LBC in the early 1950s, however, showed that some jaundice (renamed hepatitis) cases were still being transmitted through transfusions. In later years, researchers identified both hepatitis B virus and hepatitis C virus as possible contaminants in blood products . Today, all blood donors are tested for hepatitis B and C to prevent contaminated blood from being used for transfusions or for the manufacture of blood products.

Improving Existing Biologics

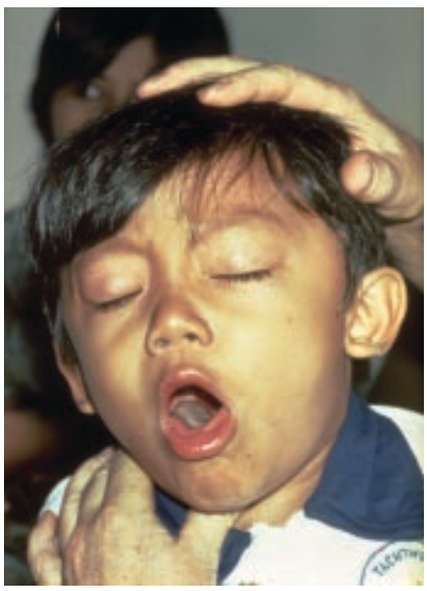
During the war years, all U.S. military personnel received shots for tetanus, typhoid fever, and smallpox. Also, tremendous quantities of vaccines for typhus, yellow fever, cholera, diphtheria, and plague as well as antitoxins and serums for various other diseases had to be manufactured to immunize those who served in areas where these diseases occur. The Division of Biologics Control had to be certain that the requirements for each product helped ensure that it would be safe, pure, and effective against the disease. In some cases, this meant improving existing products by refining standards, developing better potency tests, or finding new ways to purify a product. For instance, in 1941, the Division licensed a new vaccine for typhus—a disease caused by a kind of bacteria called rickettsia. The vaccine was given to U.S. military personnel in southern Europe and North Africa. Typhus had caused devastating epidemics in World War I, but only 64 cases occurred among U.S. military personnel in World War II.

The typhus vaccine was the first rickettsial vaccine; it was produced by growing the bacteria in fertilized hen's eggs (chick embryo), a new technique at the time. This technique was also used to make vaccines for viral diseases such as mumps. In the general effort to improve biologics, the Division of Biologics Control also conducted important research on pertussis (whooping cough) vaccine, rabies vaccine, methods for sterility testing (to assure that biologics were not contaminated by bacteria), and causes of pyrogenicity (fever reactions), particularly as related to blood products.

The Public Health Service Act (1944)

In 1944, laws relating to the Public Health Service (PHS) were revised and consolidated into the PHS Act, which helped to define the shape of medical research after World War II. The 1902 Biologics Control Act was incorporated into Section 351 of the 1944 Act with

Courtesy of National Library of Medicine



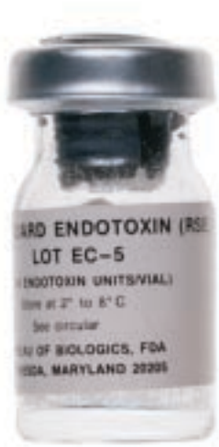
Child coughing from Pertussis infection
Courtesy of World Health Organization

Testing the Potency of Pertussis Vaccine

Pertussis, also known as "whooping cough," is a potentially deadly respiratory infection that most commonly affects children. The illness can last for weeks and is characterized by a severe cough; some infected children are left with permanent neurological damage, and some die. Although scientists had been trying to develop a pertussis vaccine since the early 1900s, the difficulty in assessing its potency was a major stumbling block. Scientists had not been able to develop a potency test for pertussis vaccine, because they were unable to establish pertussis infection in a laboratory animal. In 1944, Margaret Pittman, at the Laboratory of Biologics Control, found that she could infect mice with pertussis by injecting pertussis bacteria into the mouse brain. She then used this knowledge to test the potency of a pertussis vaccine. Pittman first gave vaccine to mice in small, medium, and large doses. Several days later, she injected them with a greater than lethal quantity of pertussis bacteria. This procedure provided the data she needed to set up a vaccine potency standard based on a "50 percent dose"—that is, the dose of vaccine that would result in the survival of 50 percent of mice infected with a certain number of pertussis bacteria. On January 1, 1949, manufacturers began using this "mouse protection test" for determining pertussis vaccine potency. Further, to make vaccine preparation easier, Pittman prepared an opacity standard for pertussis vaccine that could be used to estimate the number of bacteria in a vaccine, instead of laboriously counting the bacteria under a microscope. To do this, she adjusted the cloudiness of a suspension of glass particles until it exactly matched, as measured with an optical instrument, the cloudiness of a standard vaccine in which bacteria had been directly counted. The glass particle preparation was designated as the U.S. Opacity Standard and later was used as the International Opacity Reference Preparation. Margaret Pittman was "a woman scientist ahead of her time" and was considered a "world-renowned expert on the subject of pertussis," according to John Robbins, formerly with the Bureau of Biologics.

Pyrogenicity Testing for Blood Products

In the early 1940s, intravenous therapy using blood and blood products increased significantly because of the many wounded soldiers who needed treatment during World War II. Occasionally, pyrogenic (fever) reactions occurred after this therapy. At that time, scientists already knew that distilled water could contain pyrogens—fever-producing substances—of bacterial origin and that intravenous solutions prepared using contaminated distilled water could produce fever. In fact, by November 1942, a U.S. Public Health Service regulation required that all distilled water must be pyrogen-free. To investigate pyrogenicity in blood products, Margaret Pittman and Thomas Probey, at the Division of Biologics Control, studied the pyrogenicity of 28 types of bacteria isolated from blood plasma by using a rabbit pyrogen test. They injected the material to be tested into the ear of the rabbit. If the animal's temperature rose over the next few hours, the material was judged to be pyrogenic. Pittman and Probey found that all of the bacteria were capable of producing fever, but because the effects of various types of bacteria differed widely, simply measuring the number of bacteria in plasma could not predict the pyrogenicity of the plasma. Gram negative bacteria were the most pyrogenic of those tested. Their study also showed that bacterial growth in plasma enhanced pyrogenicity. Based on these findings, Pittman and Probey collaborated with manufacturers to help define production techniques that resulted in pyrogen-free blood products.



few changes. One important change was that the Laboratory of Biologics Control was now authorized to license biological products as well as the establishments in which they were produced. After 1944, the authority of the Laboratory of Biologics Control came from Section 351 of the 1944 Act and from certain sections of the 1938 FD&C Act. Further, the 1944 Act provided new authority for the PHS to manufacture biologics, should such a need arise. In 1948, the Laboratory of Biologics Control became part of the National Microbiological Institute within the National Institutes of Health.

A Significant Advance

One postwar research advance that significantly influenced the future of biologics was made in 1949 at Boston Children's Hospital, where scientists successfully grew a human virus—the Lansing Type II poliovirus—in human tissue cell culture. The ability to grow human viruses easily and safely outside of a living host was a breakthrough that led to an explosion of research in vaccinology, beginning in the 1950s. This advance might be considered a forerunner of the almost unimaginable discoveries and changes relevant to biologics that would occur in the second half of the 20th century.

Discovery and Change: 1950 Through 1980

The 1950s, 1960s, and 1970s were dynamic years for biologics regulation, characterized by exciting scientific advances as well as legislative and organizational changes. Vaccine research flourished because of the new techniques for growing viruses in tissue culture. The polio vaccine developed by Jonas Salk in 1954 was the first licensed vaccine made using a virus grown in this way. Preparation of vaccines for other viral diseases soon followed, including measles, mumps, rubella (German measles), and rabies. In addition, many important changes took place in testing and regulating blood and blood products. In 1972, the authority for biologics control moved from NIH to FDA. During these 30 years, the number and variety of biologics—and the challenges of regulating them—continued to grow.

Jonas E. Salk and Edward R. Murrow
Courtesy of National Library of Medicine

President Franklin D. Roosevelt and three polio patients in Warm Springs, Georgia, 1925
Courtesy of National Archives and Records Administration

The Cutter Incident

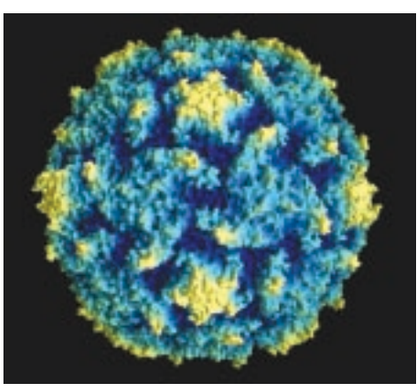
U.S. President Franklin D. Roosevelt, who suffered the paralytic effects of poliomyelitis (also called polio or infantile paralysis), initiated a "War on Polio" during his administration. He created the National Foundation for Infantile Paralysis (NFIP), a fund-raising organization, to ensure that money was available for scientists to conduct research on the cause and prevention of polio. Concerted efforts were directed toward finding a vaccine for this incurable, infectious disease. Poliovirus was successfully grown in tissue cell culture in 1949, and live poliovirus vaccine produced from virus grown by this method was successfully tested in humans in 1950. Jonas Salk, funded by NFIP, began his polio vaccine research in 1951. By 1954, a large field trial of vaccine developed by Salk, using inactivated (killed) poliovirus, was conducted in American children. Trial data showed the vaccine to be both safe and effective. On April 12, 1955, the Public Health Service issued licenses for commercial manufacture of polio vaccine to six companies that had already been producing vaccine for the field trials. Written protocols for vaccine production and safety testing, submitted to the Laboratory of Biologics Control by the companies, were the only legal requirement for licensing. Over the next two weeks, approximately 40 batches of manufactured vaccine were released by the government for distribution. Unexpectedly, on April 25, polio was reported in a vaccine recipient. One day later, five more cases were reported. All cases had received vaccine produced by Cutter Laboratories. On April 27, the Laboratory of Biologics Control requested that Cutter Laboratories recall all vaccine and the company did so immediately. On May 7, the Surgeon General recommended that all polio vaccinations be suspended pending inspection of each manufacturing facility and thorough review of the procedures for testing vaccine safety. The investigation found that live polio virus had survived in two batches of Cutter vaccine. In fact, Cutter Laboratories had discarded a number of other vaccine batches because live virus was present, but there was no requirement for them to report such difficulties. Overall, 260 cases of polio were attributed to Cutter vaccine; these included 94 vaccinees and 166 close contacts of vaccinees, with 192 cases being paralytic. Reappraisal of virus inactivation and safety testing procedures led to improved production techniques, and development of more sensitive and better-controlled testing methods to ensure consistently safe vaccine. Large-scale polio vaccinations resumed in the fall of 1955.

The Cutter Incident was a defining moment in the history of the manufacture and government oversight of vaccines. It occurred because the rigorous safety precautions that were used in the field trials—which included repeating all vaccine safety tests in three different laboratories and confirming all manufacturers' ability to prepare consistently safe vaccine—were not required for the production of commercially-produced licensed vaccine. In addition, the protocols provided by the manufacturers did not provide enough information for safety evaluation. Clearly, the government needed to strengthen its role in biologics regulation. The Cutter Incident led directly to an expansion of the Public Health Service's biologics control function. By order of the Surgeon General in 1955, regulation of biologics, which had resided in the Laboratory of Biologics Control, was transferred to the newly created Division of Biologics Standards, an independent entity within the National Institutes of Health. Also, regulations were strengthened, requiring more precise experimental testing to assess the safety of vaccines.

The Story of Polio Vaccine

A great deal of research was devoted to finding a vaccine to prevent polio. This highly contagious disease, which often had paralytic effects, affected more than 20 people per 100,000 in the United States in 1953. Anyone who was a child or a teenager before or during the early 1950s may remember not being allowed to go to crowded places such as swimming pools or movie theaters during summer or early fall, when the chances of "catching" polio were greatest. Polio was a highly publicized and greatly feared disease. The American public was extremely eager to have a vaccine.

As with all new vaccines, Salk's polio vaccine (a "killed" vaccine given by injection) had to be tested in human trials to show that it was safe and effective before it could be licensed. The National Foundation for Infantile Paralysis (NFIP) took on the responsibility for testing the polio vaccine. The Laboratory of Biologics Control had no legal role in the testing. Because of the large amount of polio vaccine needed, it was manufactured by several pharmaceutical firms. And, because these



Poliovirus Type 1 Mahoney
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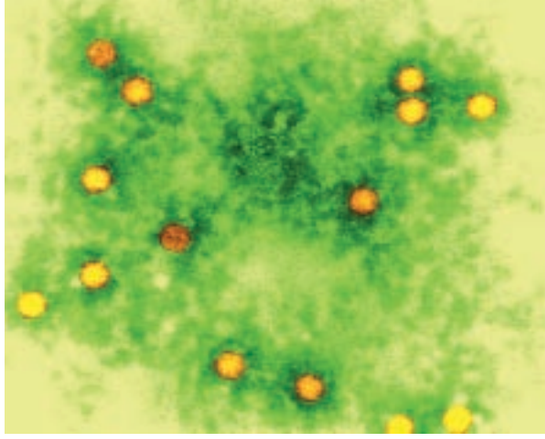

Polio Virus
Copyright Dennis Kunkel Microscopy, Inc.

firms had problems producing consistently safe vaccine—some batches of vaccine contained live virus—strict safety requirements were put into place by the NFIP, as recommended by its Vaccine Advisory Committee, a group of eminent physicians and researchers. All commercial vaccines had to be tested in three different laboratories. Also, the manufacturer had to be able to produce 11 consecutive batches of vaccine that did not contain live virus; otherwise, none of the vaccine could be used.

The field trial to test the Salk vaccine began in April 1954 in more than 1,800,000 children, the largest test using human subjects in the history of medical science. Thomas Francis, a highly respected scientist, was chosen by NFIP to design and direct the trial, and evaluate the trial results. On April 12, 1955, he reported the vaccine to be 80 to 90 percent effective, and stated that the Salk vaccine's safety was "powerfully affirmed." The Public Health Service immediately issued licenses allowing polio vaccine distribution. Unfortunately, the strict safeguards used in producing vaccine for field testing were not required in commercial production. The only legal requirement for licensing was submission of a company's written protocols for vaccine production and for safety testing to the Laboratory of Biologics Control. The rush to distribute vaccine proved to be a tragic mistake that resulted in the loss of many lives, an event known as the "Cutter Incident." Afterwards, improved production and testing procedures were implemented to ensure the safety of Salk's vaccine and, beginning in fall 1955, it was used widely in the United States.

Even though the Salk vaccine was generally successful in preventing polio, some scientists, including Albert Sabin, believed that a weakened, live-virus vaccine would provide longer-lasting immunity. Sabin developed a live polio vaccine in the mid-1950s. His vaccine, which was given by mouth, was tested in a large field trial in the Soviet Union between 1957 and 1959. By 1962, the Sabin oral polio vaccine was licensed in the United States and endorsed by the American Medical Association. It became the primary vaccine for polio prevention worldwide by the end of the 1960s. One drawback of the Sabin vaccine was a small possibility of paralysis from the live virus. By the mid-1970s, data showed that about 10 Americans per year developed paralytic polio from the live vaccine. Even so, Sabin oral vaccine continued to be used, primarily because it was the most effective means of protection for the population, but also because its oral administration was convenient. With wild polio on the brink of eradication throughout the world, in 1999 the decision was made to revert to use of an inactivated polio vaccine for routine childhood polio vaccination in the United States.

Albert B. Sabin
Courtesy of National Library of Medicine

Girl with polio in leg brace