EVENTS WITH VACCINES IN THE FIRST HALF OF THE 20TH CENTURY

The Mulkowal Disaster

In October 1902, in Mulkowal, India, 19 persons died from tetanus after being inoculated with Haffkine's inactivated parenteral whole-cell plague vaccine drawn from the same bottle. An investigative commission concluded that contamination had occurred during manufacture of the vaccine in Haffkine's laboratory in Bombay (Mumbai), India (23). Initially, Haffkine was held personally responsible and was suspended as director of the government laboratory at Bombay. Sir Ronald Ross was instrumental in releasing the report of a board of inquiry, showing that Haffkine and his laboratory were blameless (23). Under further pressure from Sir Ronald Ross, Haffkine was officially exonerated and offered the directorship of a laboratory in a government hospital in Calcutta (Kolkata). In a final vindication, in 1925, the Plague Research Laboratory of Bombay was renamed the Haffkine Institute.

The Lubeck Disaster

When BCG vaccine was initially introduced, it was administered by the oral route and was given primarily to young infants. In Lubeck, Germany, approximately 250 infants were inadvertently fed virulent *Mycobacterium tuberculosis* instead of attenuated BCG (87,88); 72 of these infants died of tuberculosis, all but one within 12 months. The virulent strain of human tubercle bacillus had been kept in the same laboratory as the stock for the BCG vaccine and had inadvertently been used instead of the vaccine strain. Investigation of the incident vindicated the safety of the BCG vaccine and initiated regulatory measures to assure proper laboratory conditions, training of personnel, and procedures in laboratories where vaccines are manufactured.

Disasters Following Diphtheria Immunization

As noted above, the earliest active immunization against diphtheria consisted of concomitant administration of mixtures of diphtheria toxin and antitoxin. Tragedies caused by efforts in manufacture were recorded in Dallas, Texas; Concord and Bridgewater, Massachusetts; Baden, Austria (86,89); Bundaberg, Russia (90); and China (91). In another instance, in Bundaberg, Australia, a diphtheria toxin-antitoxin mixture became contaminated with *Staphylococcus aureus* during manufacture of a product that contained no preservative (86,92). Of 21 children inoculated from the same bottle, 12 died of sepsis, 6 others became seriously ill but survived, while only 3 children remained healthy. *S. aureus* was isolated from abscesses in the ill but surviving children.

Typhoid Fever Following Immunization with a Heat-Treated Oral Typhoid Vaccine

In 1904, bacteriologists in the U.S. army proposed to administer killed typhoid bacilli as an oral vaccine against typhoid fever. The bacterial culture was intended to be inactivated by heating at 56°C for one hour. Initial cultures of the heated vaccine were sterile. Of 13 men who ingested the vaccine, 7 developed clinical typhoid fever and 3 others suffered ''febrile illness,'' with onsets 6 to 16 days after ingestion of the first dose of vaccine (93). Repeat bacteriological examination of the vaccine demonstrated that a few viable typhoid bacilli were recoverable (two to three organisms per milliliter).

Hepatitis Following Vaccination Against Yellow Fever

Attenuated yellow fever virus vaccine strain 17D developed by Theiler remains one of the safest and most effective vaccines ever developed. However, during World War II, it was administered to U.S. servicemen along with human immune serum. Among approximately 2.5 million troops vaccinated, 28,600 cases of icteric hepatitis occurred, leading to 62 deaths (94); it is estimated that overall approximately 300,000 infections (mostly subclinical or non-icteric) may have occurred. By means of careful epidemiological investigations and volunteer studies, it was discovered that some lots of serum used as stabilizer were contaminated with a hepatitis virus (now known to have been hepatitis B) (95,96). When human serum ceased to be given along with the yellow fever vaccine, the problem disappeared.

SOME EVENTS IN THE LATTER HALF OF THE 20TH CENTURY

The Cutter Incident

Shortly after the favorable results of the Francis field trial of Salk, inactivated poliovirus vaccine were publicized in April 1955; the FDA licensed Salk-type vaccine prepared by several manufacturers. During a 10-day period in April 1955, a total of 120,000 children were immunized with two lots of inactivated vaccine manufactured by Cutter Laboratories of Berkeley, California (97–99). Cases of poliomyelitis occurred among 60 recipients of these vaccine lots and 89 of their family members. The median incubation period for vaccinees was eight days, whereas the median incubation was 24 days for the family contacts. During faulty production, wild poliovirus did not have sufficient contact with formalin to inactivate all the virus present.

Swine Influenza Vaccine and Guillain-Barré Syndrome

In the United States in the spring of 1976, fatal influenza occurred in two individuals (one of whom was a healthy young adult) from whom a ''swine'' influenza virus (Hsw1Nl) was cultured. By serological studies, it was found that the virus antigenically resembled that of the great influenza epidemic of 1918 to 1919, which was characterized by high case fatality even in young adults. Accordingly, the U.S. Public Health Service, fearing a possible large-scale outbreak of Hsw1N1 disease in the coming winter, undertook a national program to prepare a swine influenza vaccine and to initiate a nationwide immunization campaign. The intention was to have the vaccine prepared and safety-tested and mass vaccination under way before the onset of the winter influenza season. Between October 1 and mid-December 1976, approximately 45 million doses of swine influenza vaccine were administered. However, beginning in late November and early December, reports began to appear of the occurrence of Guillain-Barré polyneuritis syndrome among recent recipients of vaccine. By December 16, the findings of a preliminary investigation corroborating this association led to a discontinuation of further immunizations with the vaccine. An extensive and detailed investigation carried out by prominent epidemiologists led by Alexander Langmuir (100) concluded that the administration of the swine influenza vaccine during the national campaign resulted in a 3.96- to 7.75-fold increase in risk of developing Guillain-Barré syndrome during the first six