general, the result of at least one such trial is required for licensure of a vaccine in most countries. One exception to this general rule has been cited above.

Historically, the development of epidemiological methods for conducting field trials to evaluate the efficacy of vaccines represented an obvious and necessary offspring of the development of new vaccines themselves. According to Cvjetanovic (25), the first attempts to determine vaccine efficacy by controlled field trials were the tests of Haffkine's live cholera vaccine in India. Initially, uncontrolled trials were carried out by Haffkine throughout India, in 1893 and 1894, involving 42,197 individuals, and, from 1895 through 1896, involving an additional 30,000 persons (81–83). However, the historic testing of his vaccine, from the epidemiological perspective, ''involved relatively small groups of individuals residing in prisons and on tea plantations'' (81–83). As reviewed by Cvjetanovic (25), Haffkine concluded that to properly assess the efficacy of his cholera vaccine, equal-sized groups of individuals should be compared, who were randomly allocated to receive vaccine or to serve as unimmunized controls and who were at essentially identical risk of exposure to natural infection.

A rigorously designed and executed large-scale vaccine field trial that included a number of the features (albeit not all) of modem-controlled vaccine efficacy trials was the evaluation by Macleod et al. (84) of a multivalent pneumococcal polysaccharide vaccine carried out among U.S. recruits at a training base during World War II. In this double-blind study in a high-risk population, 7730 persons were allocated to receive vaccine or saline placebo and surveillance was maintained for pneumococcal disease with bacteriological confirmation of clinical cases. One decade after Macleod's field trial of pneumococcal vaccine in several thousand participants, the famous Francis field trial of inactivated Salk poliovirus vaccine was undertaken in the United States, involving the inoculation of more than 650,000 children (85). The impeccably designed and executed Francis field trial constitutes a monument in the history of vaccine field trials. It incorporated all the fundamental features of modern field trial design and accomplished the logistics, data management, and data analysis in an era before computer technology, cellular telephones, and other technological aids were available. Moreover, the results of the field trial were so convincing that historic public health legislation ensued in the United States. Just a few months after announcement of the field trial results and subsequent congressional hearings (Fig. 6), the U.S. Congress passed legislation that provided financial assistance to the states in the form of grants to allow all children and pregnant women an opportunity to be vaccinated against poliomyelitis. Chapter 5 shows how much further field trial methodology has evolved from the 1940s and 1950s when Macleod and coworkers and Francis and coworkers, respectively, carried out their hallmark trials.

VACCINE CALAMITIES

An occasional byproduct of the development of new vaccines has been the inadvertent occurrence of severe adverse reactions or fatalities because of contamination, incomplete attenuation, inadequate detoxification, or idiosyncrasy. Such untoward events were obviously more common with the early vaccines. They led to an awareness of the importance of maintaining strict procedures for manufacture, testing of safety (Fig. 7), potency, purity, and (where relevant) sterility. These events also gave rise to regulatory agencies to oversee the control of biological products. Sir Graham Wilson devoted an entire book, *The Hazards of Immunization*, to this topic (86); it contains material up to the mid-1960s. Some of the more prominent disasters and incidents related to vaccines, culled from various sources, are briefly summarized below.

Figure 6 Drs. Albert B. Sabin (*left*) and Jonas Salk conferring during a press conference that followed a congressional hearing (June 22, 1955) on a bill to allocate federal funds to support vaccination of U.S. children with the inactivated polio vaccine.

Figure 7 Early animal safety test of a biological product, CSL, Parkville, Victoria, Australia. *Abbreviation*: CSL, Commonwealth Serum Laboratories. *Source*: Photo courtesy of CSL.