that, in large part as a consequence of these reactions, further work with the bilivaccine was abandoned.

Early investigators who pursued the concept of coproantibodies in the gut and local antibodies on other mucosal surfaces include Arthur Davies in the 1920s (64); Torikata and Imaizuma (65), and Theodore Walsh and Paul Cannon in the 1930s (66); and William Burrows (67) in the 1940s.

CLINICAL EVALUATION OF THE SAFETY AND EFFICACY OF VACCINE CANDIDATES

When a vaccine candidate appears, its safety must first be demonstrated in a series of small clinical trials before large-scale use of the vaccine can be considered. The need for such studies was recognized as early as the introduction of variolation in England in 1722, when royal permission was given to variolate six condemned prisoners in an effort to determine the safety of that procedure (5,8). The prisoners were offered pardon in exchange for their participation, if they survived. In November 1721, it was announced in the London newspapers that some orphan children of St. James parish, Westminster, would be inoculated as an experiment to assess the effect of variolation in children (5,6). The use of prisoners and institutionalized children for vaccine safety studies in the 1720s established a precedent that continued until the mid-1970s. For example, in the United States in the 1950s, the attenuated poliovirus vaccine was initially tested for safety and immunogenicity in adult prison volunteers (68), whereas the inactivated poliomyelitis vaccine was evaluated early on in institutionalized children (69). In the early 1970s, the ethics of experimentation in such populations, particularly prisoners, underwent reevaluation (70). A new consensus emerged that considered prisons to be inherently coercive environments in which it was difficult to guarantee informed consent (71). As a consequence, by the mid-1970s, the use of prison volunteers for phase I studies to assess the safety and immunogenicity of vaccines had virtually disappeared.

There also exists a long history of evaluating the efficacy of candidate vaccines in experimental challenge studies. In the first of Jenner's famous experiments, James Phipps, an eight-year-old boy was inoculated on the arm with cowpox. Jenner wrote (11):

> *''Not withstanding the resemblance which the pustule, thus excited on the boy's arm, bore to variolous inoculation, yet as the indisposition attending it was barely perceptible, I could scarcely persuade myself the patient was secure from the Small Pox. However, on his being inoculated some months afterward, it proved that he was secure. This case inspired me with confidence; and as soon as I could again furnish myself with Virus from the Cow, I made an arrangement for a series of inoculations. A number of children were inoculated in succession, one from the other; and after several months had elapsed, they were exposed to the infection of the Small Pox; some by Inoculation, others by variolous effluvia, and some in both ways; but they all resisted it.''*

To put Jenner's challenge of cowpox-vaccinated children with smallpox virus into proper perspective, one must appreciate that variolation was a widespread practice in England in the last quarter of the 18th century (72).

In Berlin, Germany, during the Great Depression, Wolfgang Casper, a physician who worked in the gonococcal wards of the Rudolf Virchow Hospital, developed a gonococcal vaccine consisting of a polysaccharide extract of gonococci (73). In 1930, he carried out an unusual clinical experiment to test its efficacy. Casper recruited 10 destitute individuals whom he had previously seen with gonorrhea and who had recovered (3). These 10 volunteers were moved into a ward at the hospital and provided with room and board. Five received his gonococcal vaccine and five were injected with a placebo. At a later point, a female volunteer, a prostitute, was brought onto the ward to spend one night with the 10 male volunteers, all of whom had sexual intercourse with the prostitute. Within one week, four of the five placebo recipients had developed gonorrhea versus none of the five recipients of Casper's vaccine (3).

Preliminary, small-scale clinical studies to assess the safety and immunogenicity of new candidate vaccines (phase I studies) constitute a critical first step in the evaluation of any vaccine, as is discussed in chapter 3.

Experimental challenge studies to assess vaccine efficacy represent an important step in the development of vaccines for certain infectious agents that readily respond to antimicrobial therapy or that cause self-limited illness and for which well-established models of experimental infection exist. Data from these safety, immunogenicity, and challenge studies serve to identify vaccine candidates worthy of further evaluation in large-scale field trials. In recent years, this evaluation process has been applied to vaccines against cholera (74,75), shigellosis (76), malaria (77), and influenza (78). In the modem era, there exist strict ethical guidelines to recruit the volunteers who participate in such clinical trials and to obtain their informed consent, assuring that they understand the potential risks involved and the procedures to which they will be exposed. Under sponsorship of the WHO, the Vaccine Trial Centre was established at the Faculty of Tropical Medicine of Mahidol University in Bangkok, Thailand, in the mid-1980s. This represented the first unit in a developing country where challenge studies with various pathogenic organisms could be undertaken to assess vaccine efficacy following rigorous ethical and technical local review of protocols according to international standards (79).

The relative importance of experimental challenge studies that assess vaccine efficacy in volunteers increased in 1993, when the Vaccines and Related Biologic Products Advisory Committee to the Center for Biologics Evaluation and Research of the U.S. Food and Drug Administration (FDA) voted that the results of such studies should constitute sufficient evidence of the vaccine's efficacy for submission of a Product Licensure Application. The case in point considered by the committee was the efficacy of a new live oral cholera vaccine for use in adult U.S. travelers (80). The conclusion was that the challenge studies provided a better measure of the efficacy of the vaccine for U.S. adults than would the results of a field trial in an endemic area involving a population repeatedly exposed to cholera antigens. As an earlier precedent, the efficacy of live oral cholera vaccine CVD 103-HgR as demonstrated in volunteer challenge studies was sufficient to allow the licensure of that vaccine in Switzerland, Canada, and Australia.

LARGE-SCALE FIELD TRIALS TO ASSESS VACCINE EFFICACY

In modem times, the prospective randomized, double-blind, controlled field trial under conditions of natural challenge is the definitive ''gold standard'' test of the efficacy of a vaccine. In