Subscription Information for Clinical Infectious Diseases
Published for the Infectious Diseases Society of America
SUPPLEMENT ARTICLE

From Rabbits to Humans: The Contributions of Dr. Theodore E. Woodward to Tularemia Research

Alan S. Cross, Frank M. Calia, and Robert Edelman

Center for Vaccine Development and Department of Medicine, University of Maryland School of Medicine, Baltimore

Tularemia is an endemic zoonotic infection caused by *Francisella tularensis,* which primarily causes infection in humans who have handled contaminated animal tissue or have been bitten by infected arthropods. Because of its ease of dispersion and transmission and its high degree of infectivity, *F. tularensis* is also considered to be a bioterrorism agent. Consequently, there is renewed interest in the development of safe, effective measures, such as vaccines, to prevent the morbidity and mortality associated with aerosol exposure to *F. tularensis.* Current efforts, however, are hampered by the lack of an animal model that faithfully reproduces human infection. Employing a model of "induced human infection" with aerosol administration of *F. tularensis,* Dr. Theodore E. Woodward and colleagues pioneered the clinical studies of tularemia vaccines that form the basis for current tularemia vaccine research.

In the aftermath of 11 September 2001, there has been great concern that this terrorist event may be followed by an attack with biological agents. The intentional release of anthrax through the mail later that year provided further impetus to develop both preventive and therapeutic measures against select agents that may be used in a terrorist attack. Although much attention has appropriately focused on anthrax and smallpox, after nearly a 40-year hiatus, there has been a renewed interest in the biological characteristics of tularemia and in developing measures to combat the disease. (In 2000, only 2 grants for tularemia research were funded by the National Institutes of Health. In 2005, 69 such grants were funded [M. Schaefer, National Institute of Allergy and Infectious Diseases, National Institutes of Health, personal communication]). Dr. Theodore E. Woodward and his team at the University of Maryland in Baltimore were at the forefront of early tularemia research in the United States. Dr. Woodward's interest in this infection was aroused when, as a medical student in 1938, he would walk past Lexington Market in Baltimore and observe wild rabbits dressed and hanging with noticeable spots (i.e., caseous granulomata) on their livers and abdominal contents. Not surprisingly, there was a high incidence of tularemia in Baltimore, until the City Council passed an ordinance to prohibit the sale of wild cottontails in the city. Shortly after World War II, Dr. Woodward began his lifelong association with the study of infectious diseases of military importance, the culmination of which was his guiding, for many decades, the Armed Forces Epidemiology Board (AFEB), the civilian advisory group for military medicine. Inspired by the studies of rickettsial infection conducted by Dr. Joseph Smadel, Dr. Woodward developed a human "induced infection" model for the study of tularemia. The present article will review those early studies of experimental tularemia.

ANTIBIOTIC THERAPY FOR TULAREMIA

Dr. Woodward was one of the pioneers in the study of antibiotic therapy. During the 1940s, he was among the first investigators to use chloramphenicol for the treatment of rickettsial diseases and typhoid fever, and tetracycline for plague. In their review of tularemia before the advent of antibiotic therapy, Pullen and Stuart [1] noted that the mortality rate associated with inhalational tularemia was 30%–40%. In 1957, Dr. Woodward

Reprints and correspondence: Dr. Alan S. Cross, Center for Vaccine Development, University of Maryland School of Medicine, 685 W. Baltimore St., HSF1 Rm. 480, Baltimore, MD 21201 (across@medicine.umaryland.edu).

Clinical Infectious Diseases 2007; 45:S61–7

1058-4838/2007/4502S1-0014$15.00
DOI: 10.1086/518150

argued that, because the response of most animals to experimental infection is so different from that of humans, induced infection in humans would provide the best means to investigate the effectiveness of antibiotics, evaluate vaccines, and define immune mechanisms. This approach was possible for the study of tularemia, because considerable experience indicated that there was a prompt response to streptomycin therapy after infections in laboratory animals and among laboratory personnel. In their initial human study of intradermal inoculation of virulent *F. tularensis,* Dr. Woodward and his colleagues showed that, when given too early and/or for 10 days (i.e., briefly), chloramphenicol therapy was associated with a high degree of relapse that was not observed with streptomycin therapy [2]. This important principle was also found to hold true for other intracellular infections, such as Rocky Mountain spotted fever, treated with bacteriostatic drugs.

VACCINES FOR THE PREVENTION OF TULAREMIA

Killed (Foshay) vaccine. In 1930, Foshay and colleagues [3] were the first investigators to immunize humans with a (phenolized or acetone-extracted) killed vaccine. Their study of 809 individuals immunized with this vaccine revealed that 23 (32%) of 72 vaccinated individuals who worked with tularemia acquired the disease. It was estimated that this was one-third of the number of individuals expected to acquire the disease. Of the individuals infected, 18 (78%) of 23 were considered to have mild infection [3]. By 1961, there had been >200 cases of laboratory-acquired tularemia among personnel who were immunized with the Foshay vaccine. Although 90% of naturally occurring cases of tularemia were ulceroglandular, laboratory-acquired cases were typically typhoidal, with presumed respiratory entry. By way of confirmation of Foshay's earlier data, a retrospective review of 42 cases between 1956 and 1959 suggested that only 6 of the 42 workers immunized with the Foshay vaccine had severe systemic illness, which was in sharp contrast to the responses of presumably nonimmune volunteers exposed to minimally infective doses. Thus, the killed vaccine had some limited efficacy in preventing tularemia and diminishing the severity of disease in those who became infected [4].

Live vaccine strain (LVS) vaccine. The current LVS vaccine is a descendant of strain 15 (a type B strain), which was developed by the former Soviet Union at the Gamaleya Institute in Moscow. During World War II, there was an outbreak of tularemia on the Eastern Front that involved hundreds of thousands of cases; tularemia was an alleged cause of serious disability among 10,000 Soviet troops. Although the cases of tularemia were attributed to poor sanitation, there was also the suspicion that there may have been an intentional release [5], although this was never confirmed. Mass immunization of >60 million individuals in the Soviet Union during this outbreak demonstrated the safety of the live attenuated vaccine. Although the vaccine may have been responsible for the observed reduction in the number of cases of tularemia, it is also possible that improvements in sanitation played an important role.

In one of the more extraordinary instances of Cold War cooperation between the United States and the Soviet Union, the Soviet government, in 1956, provided their live attenuated vaccine to investigators at Fort Detrick, Maryland, where it underwent further modifications for use in at-risk military personnel and laboratory workers. Eigelsbach and Downs [6] characterized various strains contained in the Russian live vaccine and determined that, among the bacterial colony types in the vaccine, a blue-colony variant was the most virulent and immunogenic. This variant was passaged through mice and was designated as the LVS. It was first used at Fort Detrick in 1959. Even though the genomes of the virulent SCHU S4 and the LVS have now been sequenced, the basis for the attenuation of LVS is still not known.

Burke [7] retrospectively compared the infection rates for personnel who received the LVS vaccine between 1960 and 1969 with the rates for these same workers who routinely received the Foshay vaccine between 1950 and 1959. He found that with the introduction of the LVS vaccine, rates of typhoidal tularemia decreased from 5.70 to 0.27 cases per 1000 at-risk employee-years; however, although the severity of the disease was milder, there was no change in the incidence of ulceroglandular tularemia [7].

EARLY STUDIES OF TULAREMIA VACCINE EFFICACY IN HUMANS

By 1955, both the Soviet Union and the United States had weaponized *F. tularensis.* The antibiotic therapy of choice at the time, streptomycin, which became available in 1949, had to be given parenterally and could not be effectively deployed in a mass exposure to *F. tularensis.* The live attenuated vaccine developed by the Russians appeared to be safe, but its efficacy was not well established. Although the retrospective evaluation of laboratory personnel suggested that the LVS vaccine may have had improved efficacy, compared with that of killed vaccines, the influence of the vaccine on the course of disease could not be evaluated, because the time, intensity, or rate of exposure of laboratory personnel to *F. tularensis* was not known. Consequently, the need for a more rigorous evaluation of vaccines for tularemia was appreciated. Studies in humans were initiated by military investigators at Fort Detrick, as well by investigators at Ohio State University (Columbus) and the University of Maryland, with the LVS vaccine provided by Fort Detrick and given in a dose of 10^9 viable organisms/mL by means of multiple punctures (i.e., scarification). The latter studies were initiated by Dr. Woodward and his colleagues as an extension of his earlier induced infection model (from 1957).

The testing of human volunteers at these sites underwent peer review and received approval from the Commissions of Epidemiologic Survey and Immunization of the AFEB, as well as from the AFEB itself. The studies were ultimately approved and funded by the Department of Defense.

In 1958, Saslaw et al. [8] examined the efficacy of the Foshay vaccine in the prevention of infection of human subjects at the Ohio State Penitentiary who were subsequently challenged intracutaneously with 10 organisms of SCHU S4 (table 1). Foshay and colleagues originally had isolated the SCHU S4 strain from a human ulceroglandular lesion in 1941. Local lesions occurred in nearly every subject. Eleven of 12 nonimmunized control subjects had systemic symptoms (7 of these 11 control subjects required antibiotics). In contrast, only 2 of 19 vaccine recipients developed systemic symptoms requiring antibiotic treatment. Subjects who received the Foshay vaccine once or who received a booster vaccine 6–8 months after initial infection exhibited symptoms of decreased severity. Interestingly, control subjects rechallenged 2–8 months after initial infection (i.e., those who were reinfected) still developed local lesions; however, they developed some protection against systemic disease. Indeed, one investigator (Francis) was reinfected 4 times [10].

These studies were followed by a comparison of the protective efficacy of the Foshay and LVS vaccines in human subjects who subsequently received aerosol challenge with 10–50 organisms of SCHU S4 [9]. Of the 29 subjects immunized with LVS (18 of whom were subsequently challenged), nearly all had transient local lesions that were followed, by 48–72 h after immunization, by nontender papules that faded by 3 weeks. One-half had transient axillary lymphadenopathy. SCHU S4 challenge was administered under carefully controlled conditions by inhalation of aerosols through masks.

In contrast to the findings from studies involving intracutaneous challenge, there was no reduction in the incidence of systemic symptoms after aerosol challenge among individuals immunized with the Foshay vaccine, compared with nonimmunized control subjects (table 1). After challenge with 10–50 organisms, 8 of 14 individuals immunized with Foshay vaccine had systemic infection, compared with 6 of 8 nonvaccinated control subjects, whereas 8 of 10 nonimmunized control subjects had systemic evidence of infection, compared with only 3 of 18 subjects concurrently immunized with LVS. Overall, 16 of 20 control subjects had systemic infection (including 2 of 2 nonchallenged control subjects). There were no positive blood culture results. Early use of streptomycin or tetracycline promptly cured the disease. The differences in protective efficacy between live and killed vaccines were not related to serum antibody titers before challenge. These studies established that as few as 10–50 SCHU S4 organisms caused tularemia when given either by aerosol or subcutaneously.

For the studies conducted by Dr. Woodward and colleagues, a special 18-wheel trailer housing a chamber that generated small-particle aerosols was developed and taken to the Maryland House of Correction in Jessup. After consent was obtained from the volunteers, infection was induced by a respiratory dispenser, and the subjects were then taken to a newly developed medical care unit in the prison.

McCrumb [11] immunized subjects intradermally with either the LVS or a nonviable, chemically fractionated cell-wall antigen (Larson) preparation, and he then exposed the subjects to SCHU S4 aerosols at 10–1000 human infectious doses (200–

Table 1. Summary of human studies comparing the protective efficacy of Foshay (killed) and live vaccine strain (LVS) vaccines against SCHU S4 challenge.

	Intracutaneous challenge with 10 cfu					Systemic symptoms after respiratory challenge with 10–50 cfu
		Systemic symptoms				
Subjects	Local lesion	Severe	Moderate	Mild	All	
Controls	12/12	7/12	3/12	1/12	11/12	14/18
Vaccine recipients						
Foshay vaccine[a]						
1 dose	12/14	1/14	0/14	3/14	4/14	8/14
2 doses	5/5	1/5	1/5	0/5	2/5	ND
LVS vaccine[b]	ND	ND	ND	ND	ND	3/18
Reinfected	8/8	0/8	1/8	1/8	2/8	ND

NOTE. Adapted from [8, 9]. Data are no. of subjects with symptoms/no. of subjects who received challenge. ND, not done.

[a] Subjects were immunized, on 3 successive days, by scarification with 0.5 mL of phenol-killed Foshay vaccine reconstituted to 7.5×10^9 organisms/mL. Subjects who received 2 doses of Foshay vaccine were boosted at 6–8 months. All groups were then challenged 3 weeks after the last immunization, including concurrently challenged control subjects.

[b] The LVS vaccine was administered by multiple intradermal punctures through a drop of rehydrated lyophilized vaccine (10^9 organisms/mL) derived only from the blue colony.

20,000 organisms)—that is, doses higher than those used by Saslaw et al. [9]. In the 10 control subjects, overt disease occurred within 3–5 days, with the incubation period affected by the size of the challenge inoculum. All control subjects had abrupt onset of fever, headache, sore throat, malaise, marked myalgia, chest tightness, and a nonproductive cough. On physical examination, pharyngeal injection and moderately severe illness were noted, with fever (temperature, 103°F–104°F) occurring during the first 24 h after infection (figure 1). McCrumb found that primary tularemic pneumonia could be induced by an aerosol with as few as 25 organisms. Four of 9 subjects immunized with the Larson vaccine (data not shown) and 10 of 14 subjects immunized with LVS (denoted by upright and stooped figures in figure 1) were protected against systemic symptoms; however, 3 of 4 LVS-immunized subjects who were not so protected were exposed to 1000 human infectious doses. Thus, Saslaw et al. [9] and McCrumb [11] independently showed the LVS vaccine to be superior to the killed vaccines in protecting against aerosol challenges of human subjects with SCHU S4. Importantly, however, McCrumb also demonstrated that, if the challenge dose was increased 10-fold, the LVS-induced protection could be overcome in ~50% of subjects.

These studies of intradermal immunization at the Maryland House of Correction were followed by studies of aerosol immunization. LVS and intermediate virulent strain 425 (similar to Eurasian strains) were administered as vaccines by aerosol in large doses. Inhaled doses of 10^6–10^8 LVS organisms produced excellent immunity against a large (e.g., 2500- to 3000-organism) SCHU S4 challenge, but 10^8 LVS organisms caused a flulike illness, with 3 of 42 subjects requiring streptomycin therapy; however, mild reactions and no disability were observed after administration of 10^6 LVS organisms. Strain 425 produced a mild form of tularemia after inhalation of 200–12,000 organisms, but no subject required antibiotic therapy. Although this strain was not suitable as a vaccine, it, too, stimulated excellent immunity against a large SCHU S4 aerosol challenge. Thus, aerosol immunization stimulated excellent protection. In these studies, Dr. Woodward also evaluated the possibility of human-to-human transmission, and he found that culture of sputum expectorated into laboratory culture

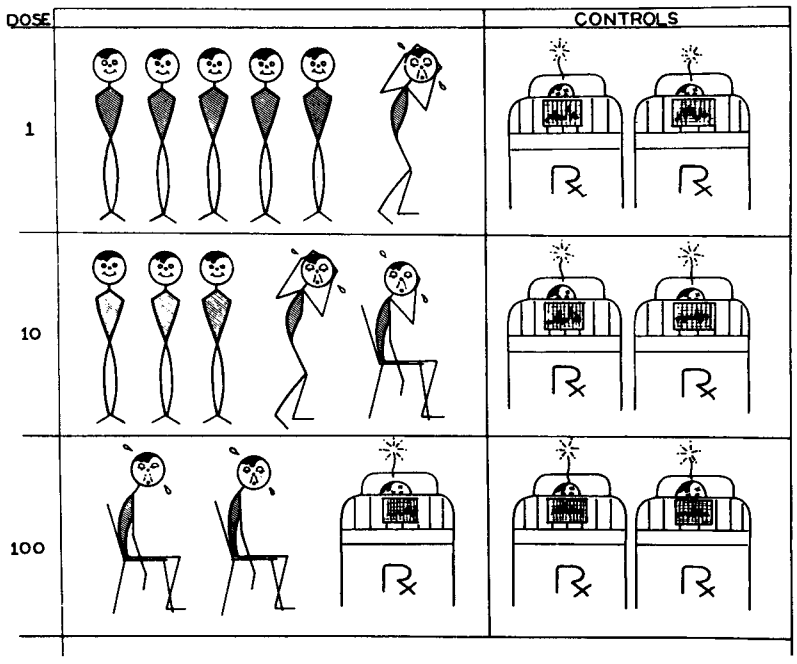

Figure 1. Protective effect of intradermal immunization with live vaccine strain (LVS) vaccine or killed (data not shown) tularemia vaccine on respiratory challenge (1–100 human infectious doses) with the virulent SCHU S4 strain. Subjects were immunized with vaccine and then were challenged by aerosol with 10–1000 human infectious doses of bacteria, corresponding to 200–20,000 organisms. The doses shown in the figure denote relative doses (each relative dose equals 10 human infectious doses [i.e., dose 1 equals 10 human infectious doses or 200 organisms]). Upright figures denote asymptomatic subjects; stooped figures, subjects with transient illness not requiring antibiotic therapy; sitting figures, subjects who exhibited symptoms but whose symptoms were ameliorated by immunization; and figures in bed, subjects whose symptoms were not modified and required treatment with antibiotics. Of the 6 subjects immunized with the killed vaccine and challenged with 10 human infectious doses (200 organisms), 3 had no symptoms, 2 had modified symptoms, and 1 required antibiotic therapy, compared with 2 of 2 nonimmunized control subjects who required antibiotics. Of the 3 subjects who received 100 human infectious doses, 1 required antibiotics, 1 had no symptoms, and 1 had modified symptoms, compared with the 2 control subjects, each of whom required antibiotics. Reprinted with permission from [11].

media by subjects exposed by aerosol to SCHU S4 did not yield positive results [12].

Although Russian studies had demonstrated that aerosol doses of 750,000 organisms could be given without ill effect, the effectiveness of these respiratory immunizations was not proved by resistance of vaccine recipients to challenge with virulent *F. tularensis.* Because McCrumb demonstrated that it was possible to overcome LVS protection with an increased aerosol dose of SCHU S4, Hornick and Eigelsbach [13] conducted a series of studies that examined the protective efficacy of respiratory immunization with LVS against aerosol and intradermal challenge with SCHU S4 (table 2). Doses of 10^4 LVS organisms were well tolerated (although all subjects had pea-sized cervical nodes), but a dose of 10^8 LVS organisms was associated with mild, self-limiting typhoidal tularemia, with 3 subjects requiring antibiotic therapy. Immunity to aerosol challenge was greater with immunization via the respiratory route than with that via the intradermal route. In these studies, as in earlier studies by Saslaw et al. [8, 9], the presence of circulating tularemia agglutinins did not correlate with resistance to infection.

In addition to administration by aerosol, LVS and the SCHU S4 strain were also administered by mouth by Dr. Woodward and colleagues. By this route, 10^8 organisms of SCHU S4 produced illness. The volunteers who gargled the organisms developed large cervical lymph nodes that rapidly responded to streptomycin therapy; however, subjects who ingested the organisms in a gelatin capsule demonstrated no reaction [12].

ETHICAL ISSUES RELATED TO RESEARCH INVOLVING PRISONERS

There were, of course, no institutional review boards (IRBs) in the 1950s, when human challenge studies of tularemia were initiated by Dr. Woodward and colleagues to test the effectiveness of antibiotics and vaccines. IRBs were formally created by an act of Congress (The National Research Act) in 1974 and by subsequent legislation. In a reminiscence written shortly before his death, Dr. Woodward addressed IRBs and other ethical concerns about tularemia research involving human subjects, particularly prisoners [14]. Given his previous findings regarding the differences among animal species in their response to *F. tularensis,* Dr. Woodward concluded that answers to the question of whether antibiotics or vaccines were effective in the treatment or prevention of tularemia in humans could only be answered in studies of human subjects. Initially, Dr. Woodward used members of his staff or volunteer patients from the wards of the medical service for intradermal challenge studies. Subsequent studies were performed on inmates in the state penitentiaries in Maryland and Ohio, under the sponsorship of the Department of Defense. During World War II, to develop treatments for infectious diseases, voluntary research programs were initiated in prisons by several federal agencies. Such research, which the public considered to be acceptable and praiseworthy and the prisoners themselves considered to be patriotic, continued after the conclusion of the war. Indeed, passage of the Kefauver-Harris amendment to the Food and Drug Act in

Table 2. Summary of studies comparing respiratory and intradermal immunizations with live vaccine strain (LVS) vaccine, followed by challenge with SCHU S4.

LVS immunization/SCHU S4 challenge	Subjects who received challenge, no.	Infected subjects,[a] no. (%)	Subjects requiring antibiotic treatment, no. (%)	Subjects protected against disease,[b] no. (%)
Respiratory/respiratory				
Aerogenic	102	71 (70)	23 (23)	79 (77)
Control	47	44 (94)	42 (89)	
Respiratory dose-response[c]/respiratory				
10^8 cfu LVS	30	18 (60)	0	30 (100)
10^6 cfu LVS	16	10 (63)	0	16 (100)
10^4 cfu LVS	56	43 (77)	23 (41)	33 (59)
Dermal	46	29 (63)	21 (46)	25 (54)
None	47	44 (94)	42 (89)	
Respiratory/intradermal				
Dermal	24	NS	4 (17)	20 (83)
Respiratory	14	NS	2 (14)	12 (86)
Control	19	NS	19 (100)	0

NOTE. Adapted from [13]. Subjects were immunized with 10^4–10^8 cfu of LVS and were challenged with 25,000 cfu of SCHU S4 (i.e., >2500 minimum human infective doses).

[a] With infection defined as a temperature ⩾100°F

[b] With disease defined as a temperature of 103°F for 24 h.

[c] Vs. intradermal.

1962, which established additional requirements for safety and efficacy testing, encouraged the continued use of prisoners in research.

For Dr. Woodward's studies, a laboratory safety hood and aerosol chamber were transported to the Maryland House of Correction. The clinic at the facility was upgraded for the studies, and the medical supervision that was provided exceeded that available to other prison inmates. As was previously noted, given the prompt response to antibiotic therapy, no subject had any symptom (mild fever and headache, small primary lesion, or moderate lymph node enlargement) last beyond 24 h after challenge, and there were no serious adverse events. In 1967, investigators (including F.M.C.) performed additional studies at Fort Detrick in which Seventh Day Adventists, all of whom were college graduates, were recruited as volunteers under the supervision of the AFEB [15]. In those studies, the consent process was recorded; written, informed consent was obtained, and subjects were required to take pre- and postconsent process examinations before enrollment. At the time, this was one of the most rigorous consent processes for studies of human subjects.

Dr. Woodward was cognizant of the ethical issues raised by the conduct of biomedical research in prison populations. All testing of volunteers was subject to peer review, with approval required by the Commissions of Epidemiologic Survey and Immunization of the AFEB and by the AFEB itself. The Department of Defense then ensured that the studies were conducted according to Army Regulation 70-25 (1962), which governed the use of volunteers as research subjects. Fully informed, written consent was obtained without coercion or any inducements (such as financial rewards or a reduction in the length of prison terms), and the subjects were free to withdraw at any time and were fully informed of medical developments. In 1974, Dr. Woodward was legally required to terminate the volunteer program at the Maryland House of Correction, when the American Civil Liberties Union filed a class action suit against Dr. Woodward, his research team, the University of Maryland, and all state and federal governmental sponsors of the research. The suit claimed, in part, that incarcerated prisoners are innately vulnerable to coercion and cannot really provide free consent in a prison environment. Initially, the judge rejected the case brought by the American Civil Liberties Union and remarked that the research team employed high ethical standards and that the research was of considerable value to the public and the military service. However, in 1977, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research recommended that research involving prisoners should not be conducted in the United States unless the research uniquely and directly benefits the prison volunteer or other prisoners as a class. Starting in 1977, the recommendation found its way into a series of Department of Health and Human Services regulations [16]. These regulations, in effect, terminated infectious diseases research involving US prison volunteers, except for those conditions particularly affecting prisoners as a class, such as hepatitis. However, today, an IRB could approve similar tularemia challenge studies in nonprison volunteers, so long as fully informed, written consent was provided and the IRB judged that benefits to the volunteers or to society would clearly outweigh the risk to the volunteers. Remember that ~500 human subjects were challenged with virulent SCHU 4 *F. tularensis* without any reports of serious adverse effects, and that, as we enter the 21st century, we confront the real threat of bioterrorism.

CONTRIBUTION OF THE EARLY STUDIES OF EXPERIMENTAL HUMAN TULAREMIA TO THE CURRENT DEVELOPMENT OF VACCINES FOR TULAREMIA

What is the legacy of this work? We know the infectious doses for humans when they are given either by aerosol or intradermally and that early antibiotic therapy is effective clinically. Furthermore, early studies demonstrated that a live attenuated vaccine provides protection against *F. tularensis* challenge by both aerosol and intradermal routes. Thus, although the role of specific host defense mechanisms necessary for protective immunity against *F. tularensis* is incompletely understood, early studies demonstrated that a cellular immune response is required for durable immunity. Nevertheless, although these studies established that the induction of serum antibodies by killed vaccines did not prevent infection, the induction of serum antibodies did have some degree of efficacy in preventing the symptoms of systemic tularemia. Importantly, increasing the aerosol challenge can overcome LVS-induced protection. This finding has provided the impetus for the development of live attenuated strains of SCHU S4, which is currently under way in several laboratories. These early studies also demonstrated that immunization by aerosol and oral (i.e., mucosal) routes was safe (at a dose of $\leqslant 10^6$ organisms) and effective. This might be important in the event of a need for mass immunization when immunization by the current scarification method would be impractical. In the absence of any animal model that faithfully reproduces tularemia in humans, these valuable insights from an earlier era will certainly guide the further development of tularemia vaccines.

Acknowledgments

A.S.C. and R.E., during their careers in the military, knew Dr. Woodward during his tenure on the Armed Forces Epidemiology Board, Later, on joining the faculty at the University of Maryland, they both enjoyed many conversations with Dr. Woodward during his "active retirement." R.E. is chairman of the institutional review board at the University of Maryland. F.M.C. is the Theodore E. Woodward Professor of Medicine at the University of Maryland. We thank Dr. Sheldon Greisman, a colleague of Dr. Woodward for many years, for his careful review of this manuscript.

Financial support. National Institutes of Health (grant U54 AI057168-01 to A.S.C. for research on tularemia).

Supplement sponsorship. This article was published as part of a supplement entitled "Tribute to Ted Woodward," sponsored by an unrestricted grant from Cubist Pharmaceuticals and a donation from John G. McCormick of McCormick & Company, Hunt Valley, Maryland.

Potential conflicts of interest. R.E. is a paid consultant to Acambis. All other authors: no conflicts.

References

1. Pullen RL, Stuart BM. Tularemia: analysis of 225 cases. JAMA **1945**; 129:495–500.
2. McCrumb FR Jr, Snyder MJ, Woodward TE. Studies on human infection with *Pasteurella tularensis:* comparison of streptomycin and chloramphenicol in the prophylaxis of clinical disease. Trans Assoc Am Physicians **1957**; 70:74–9.
3. Kadull PJ, Reames HR, Coriell LL, Foshay L. Studies on tularemia. V. Immunization of man. J. Immunol **1950**; 65:425–35.
4. Overholt EL, Tigertt WD, Kadull PJ, et al. An analysis of forty-two cases of laboratory-acquired tularemia: treatment with broad spectrum antibiotics. Am J Med **1961**; 30:785–806.
5. Alibek K. Biohazard. New York: Dell, **1999**:29–31.
6. Eigelsbach HT, Downs CM. Prophylactic effectiveness of live and killed tularemia vaccines. I. Production of vaccine and evaluation in the white mouse and guinea pig. J Immunol **1961**; 87:415–25.
7. Burke DS. Immunization against tularemia: analysis of the effectiveness of live *Francisella tularensis* vaccine in prevention of laboratory-acquired tularemia. J Infect Dis **1977**; 135:55–60.
8. Saslaw S, Eigelsbach HT, Wilson HE, Prior JA, Carhart S. Tularemia vaccine study. I. Intracutaneous challenge. Arch Intern Med **1961**; 107: 689–701.
9. Saslaw S, Eigelsbach HT, Prior JA, Wilson HE, Carhart S. Tularemia vaccine study. II. Respiratory challenge. Arch Intern Med **1961**; 107: 702–14.
10. Francis E. Immunity in tularemia. Trans Assoc Am Phys **1936**; 51: 394–8.
11. McCrumb FR. Aerosol infection of man with *Pasteurella tularensis.* Bacteriol Rev **1961**; 25:262–7.
12. Woodward TE. Early studies on tularemia and plague. In: Woodward TE, ed. Research on infectious diseases at the University of Maryland School of Medicine & Hospital: a global experience 1807 to 2000. Baltimore: Medical Alumni Association of the University of Maryland, **1999**:77–85.
13. Hornick RB, Eigelsbach HT. Aerogenic immunization of man with live tularemia vaccine. Bacteriol Rev **1966**; 30:532–8.
14. Woodward TE. Early studies on tularemia and plague. In: Woodward TE, ed. Research on infectious diseases at the University of Maryland School of Medicine & Hospital: a global experience 1807 to 2000. Baltimore: Medical Alumni Association of the University of Maryland, **1999**:142–3.
15. Pekarek RS, Bostian KA, Bartelloni PJ, Calia FM, Beisel WR. The effects of *Francisella tularensis* infection on iron metabolism in man. Am J Med **1969**; 258:14–25.
16. Federal Register, Department of Health, Education, and Welfare. Protection of human subjects: research involving prisoners. **1977**; 42: 3076–91.